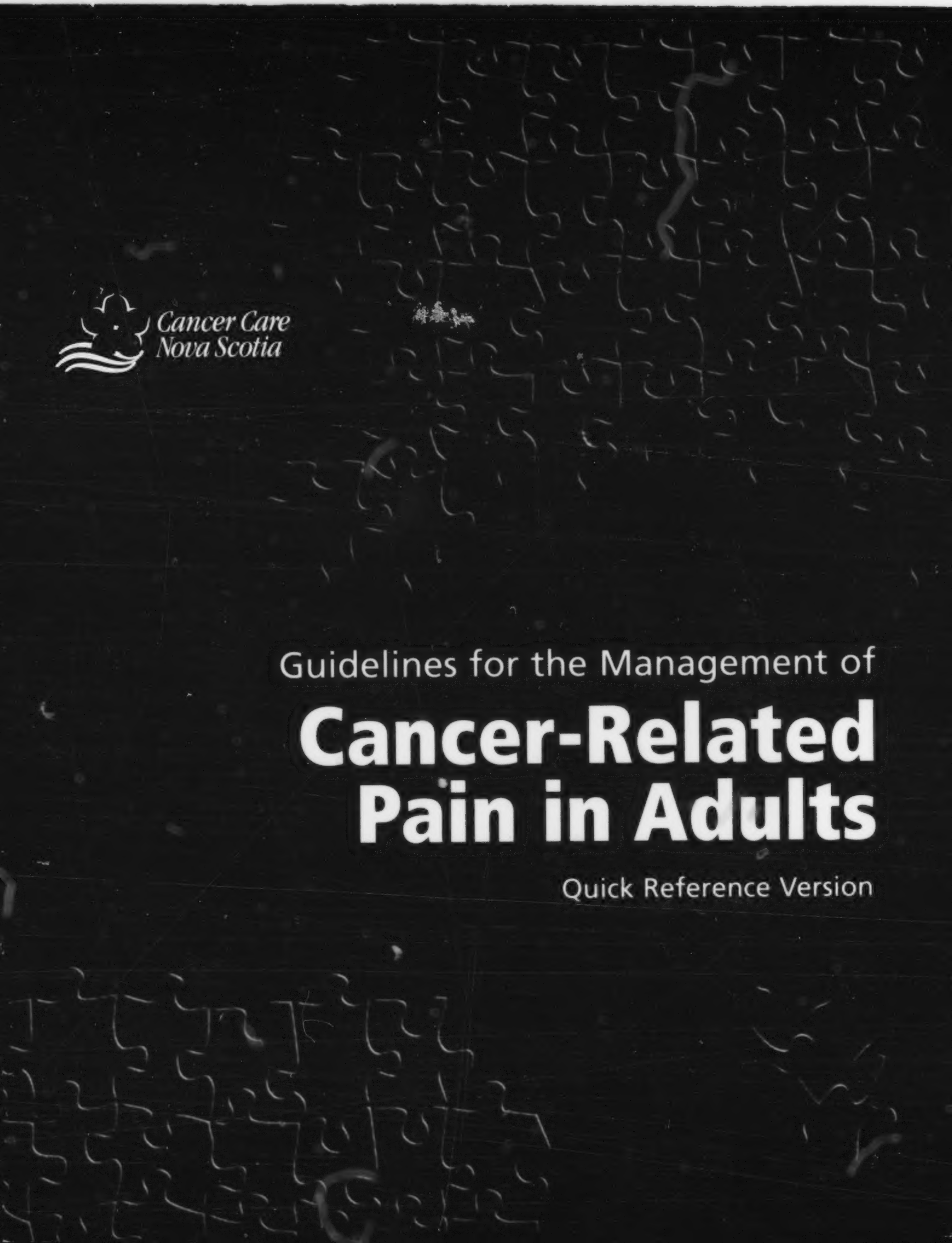

Cancer Care
Nova Scotia

Guidelines for the Management of

Cancer-Related Pain in Adults

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Best Practice Guidelines for the Management of

Cancer-Related Pain

In Adults

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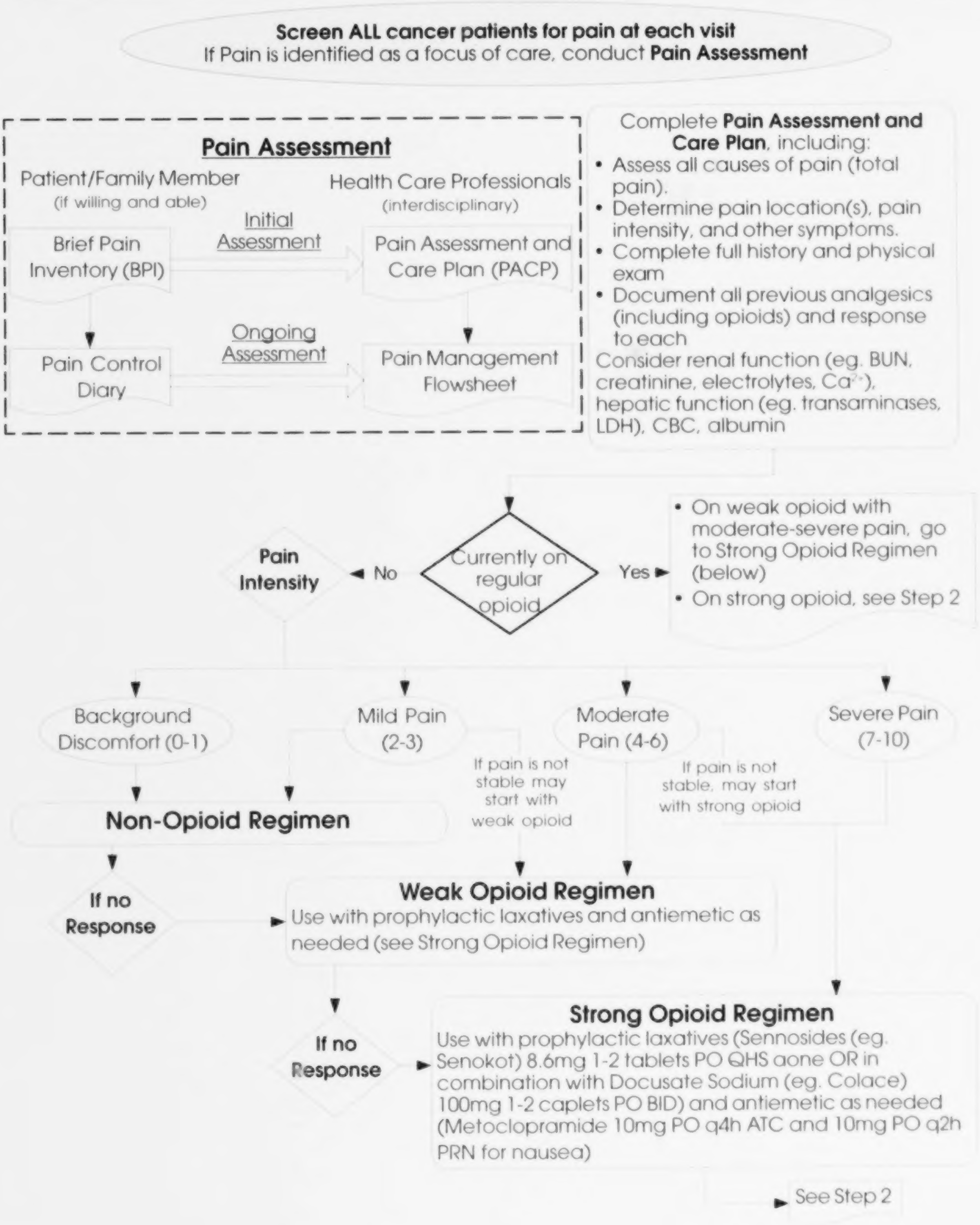
Treatment of Cancer Pain - Step 1



Screen ALL cancer patients for pain at each visit
If Pain is identified as a focus of care, conduct **Pain Assessment**

Pain Assessment

Patient/Family Member (if willing and able)

Health Care Professionals (interdisciplinary)

Brief Pain Inventory (BPI) → Initial Assessment → Pain Assessment and Care Plan (PACP)

Pain Control Diary → Ongoing Assessment → Pain Management Flowsheet

Complete **Pain Assessment and Care Plan**, including:

- Assess all causes of pain (total pain).
- Determine pain location(s), pain intensity, and other symptoms.
- Complete full history and physical exam
- Document all previous analgesics (including opioids) and response to each

Consider renal function (eg. BUN, creatinine, electrolytes, Ca^{2+}), hepatic function (eg. transaminases, LDH), CBC, albumin

Currently on regular opioid

Yes

- On weak opioid with moderate-severe pain, go to Strong Opioid Regimen (below)
- On strong opioid, see Step 2

No

Pain Intensity

Background Discomfort (0-1)

Mild Pain (2-3)

If pain is not stable may start with weak opioid

Moderate Pain (4-6)

If pain is not stable, may start with strong opioid

Severe Pain (7-10)

Non-Opioid Regimen

If no Response

Weak Opioid Regimen
Use with prophylactic laxatives and antiemetic as needed (see Strong Opioid Regimen)

If no Response

Strong Opioid Regimen
Use with prophylactic laxatives (Sennosides (eg. Senokot) 8.6mg 1-2 tablets PO QHS aone OR in combination with Docusate Sodium (eg. Colace) 100mg 1-2 caplets PO BID) and antiemetic as needed (Metoclopramide 10mg PO q4h ATC and 10mg PO q2h PRN for nausea)

See Step 2

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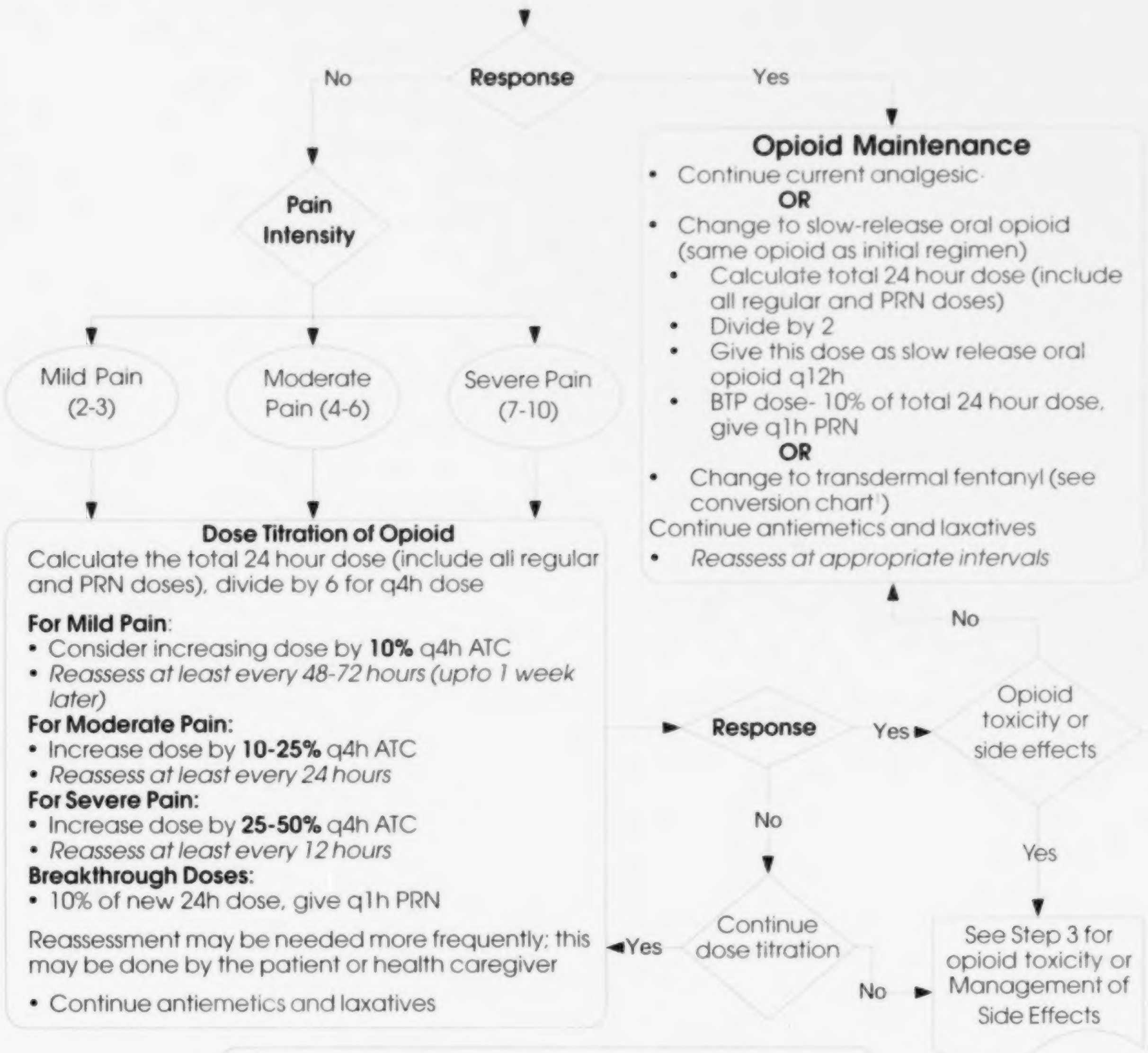
Treatment of Cancer Pain - Step 2

Strong Opioid Regimen (from Step 1)

- Morphine 5 mg PO or 2.5 mg SC / IV q4h ATC[2] and 2.5 mg PO or 1.25 mg SC / IV q1h PRN BTP[2] - **OR**
- Hydromorphone 1 mg PO or 0.5 mg SC / IV q4h ATC and 0.5 mg PO or 0.25 mg SC / IV q1h PRN BTP - **OR**
- Oxycodone 5 mg PO q4h ATC and 2.5 mg PO q1h BTP - **OR**
- Acetaminophen 325mg & Oxycodone 5mg (eg. Percocet) 1-2 tablets q4h ATC and 1 tablet q2h BTP; not to exceed 12 tablets per day
- Use with prophylactic laxatives (Sennosides (eg. Senokot) 8.6mg 1-2 tablets PO QHS alone OR in combination with Docusate Sodium (eg. Colace) 100mg 1-2 caplets PO BID) and antiemetic as needed (Metoclopramide 10mg PO q4h ATC and 10mg PO q2h PRN for nausea)



Opioid Maintenance

- Continue current analgesic

OR

- Change to slow-release oral opioid (same opioid as initial regimen)
  - Calculate total 24 hour dose (include all regular and PRN doses)
  - Divide by 2
  - Give this dose as slow release oral opioid q12h
  - BTP dose- 10% of total 24 hour dose, give q1h PRN

OR

- Change to transdermal fentanyl (see conversion chart[1])

Continue antiemetics and laxatives

- *Reassess at appropriate intervals*

Dose Titration of Opioid

Calculate the total 24 hour dose (include all regular and PRN doses), divide by 6 for q4h dose

For Mild Pain:
- Consider increasing dose by **10%** q4h ATC
- *Reassess at least every 48-72 hours (upto 1 week later)*

For Moderate Pain:
- Increase dose by **10-25%** q4h ATC
- *Reassess at least every 24 hours*

For Severe Pain:
- Increase dose by **25-50%** q4h ATC
- *Reassess at least every 12 hours*

Breakthrough Doses:
- 10% of new 24h dose, give q1h PRN

Reassessment may be needed more frequently; this may be done by the patient or health caregiver

- Continue antiemetics and laxatives

See Step 3 for opioid toxicity or Management of Side Effects

Consider consult to palliative care service/ pain specialist

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Treatment of Cancer Pain - Step 3

Opioid toxicity or side effects[1]

Management Options[2]

Opioid Rotation

Opioid rotation is changing from one opioid to another opioid. Opioid rotation may be considered if pain is or has been relieved with original opioid, but actual or predicted toxicity limits further dose titration.

- Select an alternate opioid
- Calculate equianalgesic equivalent dose of new opioid- See Conversions (below)
- Adjust starting dose of new opioid-consider decreasing initial dose by 25-50% if pain controlled by old opioid (no reduction if pain not controlled by old opioid)
- Titrate dose, as in Step 2

NOTE: It is strongly recommended that Meperidine (Demerol), Pentazocine (Talwin) or Propoxyphene (Darvon) **NOT** be used for cancer pain management

Addition of Adjuvant(s)

Adjuvant agents may be considered to augment the analgesic effect of an opioid, or to produce analgesia by a different mechanism. Adjuvant agents may be considered for malignant bone pain, neuropathic pain, incident pain, pain from compression or distension of tissues, or other related pain problems.

- Adjuvant analgesic agents and doses (See page 117 in Full Version)

Opioid Dose Reduction

Reduction of dose may be considered instead of opioid rotation if it is suspected that the opioid toxicity is due to excessive dosage and pain may be controlled with a lower dose.

- Careful dose reduction may eliminate opioid toxicity- Monitor pain control
- Dose reduction may include the concurrent addition of adjuvant analgesics

Change Route of Opioid

Sometimes changing the route of administration may reduce toxicity or side effects. Consider changing administration route if there are absorption concerns or if the oral route is limited by symptoms (eg. nausea or vomiting). Choice of alternate route is a clinical decision.

- Routes of administration include oral (recommended first choice), rectal or parenteral (eg. subcutaneous, intravenous), transmucosal (eg. sublingual/buccal, nasal) or transdermal.

Manage Side Effects or Opioid Toxicities

See Management of Side Effects from Opioid Therapy- Page 5

Consider consult to palliative care service/ pain specialist

NOTES

1. Opioid toxicity refers to symptoms related to opioid dose (eg. neurological symptoms) whereas side effects are symptoms which may occur at any opioid dose (eg. constipation), see full version for more details
2. See full version of the guideline for discussion of management options and criteria for selection

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Opioid Dose Conversions

Opioid Equianalgesic Dose Conversions

Drug	Oral Dose	Parenteral Dose	Ratio PO to IV/SC	Ratio PO to Morphine PO
Morphine*	20 mg	10 mg	2:1	1 : 1
Hydromorphone*	4 mg	1 mg	2 : 1	1 : 5
Oxycodone	15 - 20 mg	20 mg	1 or 1.5 : 1	1.5 or 2 : 1
Codeine	200 mg	120 mg	2 : 1	12 : 1
Levorphanol	4 mg	2 mg	2 : 1	1 : 5
Oxymorphone	5–10 mg (PR)1 – 1.5 mg	1:3 to 1:10	1 or 1.5 : 10	
Fentanyl	For conversion to transdermal dose, see Transdermal Fentanyl Dosing Table below			
Methadone	For conversion, see Dosing of Oral Methadone in Full Version			

Dosing of Transdermal Fentanyl

- To convert from an opioid to transdermal fentanyl (Duragesic), first calculate the 24 hour oral morphine equivalent dose, then locate the equivalent fentanyl dose on the chart below
- Continue the original opioid for 12-24 hours after the first transdermal patch is applied, to allow the patch to create a reservoir under the skin

Transdermal Fentanyl Dose Conversion from Morphine

Oral Morphine Dose per 24 hrs.	Parenteral Morphine Dose per 24 hrs.	Fentanyl Patch Dose (mcg/hr)
45-134 mg	15-44 mg	25
135-224 mg	45-74 mg	50
225-314 mg	75-104 mg	75
315-404 mg	105-134 mg	100
405-494 mg	135-164 mg	125
495-584 mg	165-194 mg	150

- For ease of conversion, consider 50-100 mg of oral morphine in 24 hours equal to 25mcg/hr transdermal fentanyl
- Breakthrough opioid medication- use 5-10 mg morphine/ 1-2 mg hydromorphone q1 hr PRN for each 25 mcg/hr fentanyl

Dosing of Oral Methadone for Cancer Pain

- Prescribers are required to have a methadone licence (from Health Canada) to prescribe this agent
- It is suggested to consult with a prescriber with methadone expertise when considering the use of methadone
- Equianalgesic conversion ratios from other opioids to methadone may vary based upon the dose of the opioid at time of conversion
- There are several methods for converting from another opioid to methadone. See the **Full Version** of this guideline for details on conversion

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Management of Side Effects/Toxicities from Opioid Therapy

Management of Common Side Effects and Opioid Toxicities

Nausea and Vomiting

- Prophylactic treatment of nausea not recommended
- If nausea is a consistent problem, consider prokinetic antiemetic drugs (metoclopramide or domperidone 5-20 mg PO TID-QID)

See *CCNS* Guideline on Management of Nausea & Vomiting

Constipation

- Continue prophylactic dose of 1 to 2 sennoside 8.6mg tablets QHS with/without stool softener (docusate)
- Increase dose of sennoside (up to 12 tablets daily) and/or Docusate (up to 8 caplets daily) - divided doses
- Consider addition of Lactulose (15-30 mL PO BID, then titrate as required)
- Consider use of Bisacodyl, laxative enemas or suppositories

Sedation

- Consider rotation or dose reduction of opioid
- Assess for other sedating medications
- Assess for other causes for sedation (eg. exhaustion, metabolic disorders,)
- Consider steroids- Dexamethasone 4-8 mg PO/ SC QD
- Consider psychostimulant- Methylphenidate (Ritalin) 2.5-5mg PO QD-BID

Neurological Symptoms (eg. myoclonus, hyperalgesia/alodynia, hallucinations, delirium, nightmares)

- Consider rotation or dose reduction of opioid
- Consider reversible causes (eg. metabolic disorders, liver or renal dysfunction) or irreversible causes (eg. organic brain disease)
- Specific symptoms:
  - Myoclonus- Consider Clonazepam 0.5-1 mg PO QD-TID or Valproic Acid 5 mg/Kg PO TID (increase in increments of 5-10 mg/Kg/day)
  - Nightmares- Consider Clonazepam 0.5-1 mg PO QD-TID, Haloperidol 2.5-5 mg HS
  - Hallucinations- Consider Haloperidol 1-5 mg q4h PRN
  - Delirium or agitation- Consider Haloperidol 2.5-5 mg PO/SC q6-12h PRN or Midazolam 2-5 mg SC stat then 30 mg/24 hr SC infusion or 5 mg SC q1h

Consider consult to appropriate specialist (eg. palliative care service/ pain specialist) for specific symptoms

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Management of Pain Crisis

Pain crisis may occur with any patient at any point in time. Pain crisis is acute, severe pain which is overwhelming and exceeds the coping strategies of the patient and family. During crisis, there is no time for the usual dose titration. Pain crisis is an **emergency** situation.

Identification of Pain Crisis

1. Patient/family call
2. Telephone assessment and advice to patient (by attending physician or nurse to determine if crisis and to suggest immediate measures until visit)

Calls may be to:

1. Family doctor or other attending physician or nurse
   - After hours- call physician, if on-call available
2. Palliative care or oncology service, if attending with this service
   - After hours- call service , if on-call available
3. Emergency room- only if no other call is available

Patient Visit

- Urgent visit- arrange as soon as possible (do not defer)
- Preferably within 1 to 2 hours of call

Assessment

- Assess pain level and recent history (including medications)
- Assess distress level and recent history of distress

Treatment of Pain Crisis

Manage BOTH pain and distress

New Pain Syndrome

Identify any specific syndromes (e.g. spinal cord compression, SVC syndrome)

- Treat as per guidelines appropriate to specific syndrome(s)

Exacerbation of Underlying Pain

- No new pain pathology
- Rapid titration of short-acting opioid (e.g. Morphine 5-10 mg or Hydromorphone 1-2 mg SC/IV -not PO; repeat q10 min PRN for ongoing severe pain)
- Titrate until pain relief or sedation

Distress

- Anxiolytic agent for acute distress (parenteral route preferred)
- Treatment plan per *CCNS* Distress Management Guideline

EXAMPLE

- Calculate the total 24 hour opioid dose (include all regular and PRN doses), increase by 25-50%, divide by 6, convert to parenteral equivalent (usually 50% of oral dose); Give this as a bolus opioid dose SC and give lorazepam 0.5-1 mg SC or midazolam 1mg (up to 5 mg) SC for immediate distress management
- Repeat doses of both opioid and anxiolytic agent q30 minutes until pain relief or sedation intervenes
  - Maximum 3 doses of each agent- if no relief, re-assess and consider palliative care/pain specialist consultation
- Caution- monitor respiratory rate, and SaO_2 (if available)
  - If respiratory depression with low O_2 saturation, adminster O_2, provide verbal & tactile stimulation; if inadequate response consider giving low dose naloxone (0.4 mg diluted in saline to 10 mL, give 1 mL q1-2 minutes until adequate SaO_2)

Follow-Up

- Consider admission to hospital until pain crisis is stabilized (unless patient is actively dying or wishes to remain at home)
- When pain crisis is stabilized, recalculate new q4h dosing of opioid
- Reassess within 24 hours of stabilization of pain crisis; educate patient/family on new expectations
- Refer to appropriate other services for long-term distress management

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Management of Special Pain Problems

Spasms (cramps)

For muscular or skeletal spasms:
- Baclofen 5 mg PO TID (may titrate q3d up to 20 mg PO TID)
- Diazepam 2 mg PO TID (may titrate up to 10 mg PO TID)
- Midazolam 1-3 mg SC q30 min PRN (or lorazepam 0.5-2 mg SC q1 hr PRN)

For visceral spasms or cramps:
- Loperamide 1-2 mg PO TID to QID
- Buscopan (hyoscine butylbromide) 10 mg PO TID-QID
- Scopolamine patch 1.5 mg transdermally q3d
- Glycopyrrolate 0.2-0.4 mg SC q4-8h
- Consider Octreotide 200 mcg SC q8h (may increase to 800 mcg)

Post-Radiation Pain

Acute Pain Problems (e.g. burns)
- Most radiation-induced pain responds to usual opioid therapy; see Steps 1 & 2 (pages 108-109 in Full Version)
- If severe, consult with radiation oncologist for management

Pain Flares
- Rapid upward titration of opioid when pain increases
- Careful monitoring, decrease opioids when pain decreases

Chemotherapy-Related Pain Syndromes

Drug-Related Neuropathies
- Consult with oncologist (chemotherapy may be altered)
- Treatment like neuropathic pain (see page 117 in Full Version)
- Educate patient/family
- Explore psychosocial support groups, complementary treatment options

Hand-Foot Syndrome (Palmar-Plantar Erythrodysaesthesia)
- Consult with oncologist (chemotherapy may be altered)
- Symptomatic relief with topical moisturizing creams (e.g. BagBalm, Udder Cream)

Mucositis Pain
- See ***CCNS*** **Guidelines for the Management of Oral Complications from Cancer Therapy**

Chronic Pain in Cancer Patients

- Cancer patients may also suffer from pain due to other causes
- Treat each type of pain, as appropriate
- Pain may be due to cancer treatment (e.g. surgery, radiation therapy)
- Consider referral to appropriate sub-specialist (e.g. gastroenterology, neurology, urology, ENT), or pain specialist
- Consider non-pharmcological approaches (e.g. physiotherapy, nerve blocks, TENS, distraction methods, guided imagery)
- Consider appropriate support groups

Consider consult to appropriate specialist (eg. palliative care service/ pain specialist)

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Adjuvant Therapies

In addition to optimal opioid therapy and cancer treatment, if appropriate

Malignant Bone Pain ►

Acetaminophen 325-650 mg q4h PO
- To a maximum of 4 g/day *(less with renal or hepatic impairment)*

AND/OR

Non-Steroidal Anti-Inflammatory Agent PO (NSAID)
- Common Examples:
  - Ibuprofen 200-800 mg TID (available without prescription)
  - Naproxen 250-500 mg BID
  - Diclofenac 25-50 mg TID or 75 mg SR daily
  - Celecoxib 100-200 mg QD-BID
- May co-administer cytoprotectant agent (eg. Misoprostol) in patients with risk of ulceration or concurrently on NSAIDs and steroids

AND/OR

Corticosteroid
- Dexamethasone 4 mg PO qAM (may use higher or lower doses)
- May be added to NSAID/Acetaminophen, or replace NSAID
- Use cytoprotectant if corticosteroid and NSAID given concurrently
- Plan use for limited period, monitor for effects; taper dose to discontinue

AND/OR

Bisphosphonate
- Pamidronate 60-90 mg IV or Zoledronic Acid 4-8 mg IV every 3-4 weeks

AND/OR

Non-Pharmacologic Approaches:
Consider radiotherapy, physiotherapy, prophylactic subluxation, or fixation (if fracture present)

Neuropathic Pain[1] ►

Tricyclic Antidepressant
- Amitriptyline 10 to 25 mg qHS
- Nortriptyline 10 to 25 mg qHS or Desipramine 25 mg qHS *(fewer anticholinergic side effects)*

AND/OR

Antiepileptic drugs
- Gabapentin 100-300 mg qHS
- Carbamazepine 100-200 mg BID
- Valproate 250 mg daily to TID

AND/OR

Corticosteroid (as above)

AND/OR

Ketamine 5-10 mg PO BID (refer to pain specialist for initiation and titration)

AND/OR

Non-Pharmacologic Approaches:
- Consider radiotherapy, surgical decompression, TENS, nerve blocks

Note: drug listings are examples with suggested starting doses

Incident Pain (Pain on mobilization) ►

Sufentanil 25-50 mcg SL/buccal, **Fentanyl** 50 mcg SL/buccal prior to mobilization

Non-Pharmacologic Approaches:
- Sling, splint, crutches, cane, walker, physiotherapy/occupational therapy

Pain from Compression or distention of tissues ►

Corticosteroid (as above)

AND/OR

Non-Pharmacologic Approaches: Consider radiotherapy, surgical decompression

1. Methadone may be a more effective opioid in neuropathic pain treatment
See: Table 5.22 in Full Version for more details on drug dosing

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Cancer Care
Nova Scotia

Guidelines for the Management of

Cancer-Related Pain in Adults

Full Version

Cancer Care
Nova Scotia

Best Practice Guidelines for the Management of
Cancer-Related Pain
In Adults

Best Practice Guidelines for the Management of Cancer-Related Pain in Adults

Objective:

This guideline will review pain assessment and management in adult cancer patients. Evidence will be reviewed and recommendations made for assessment, treatment and other management issues. A simplified discussion with flowcharts (practice pathways) will summarize the written contents. Through improved knowledge of health care professionals, it is expected that cancer pain management may be improved.

One specific objective for this guideline is to **standardize the assessment of cancer-related pain in adults across Nova Scotia**. By creating a common approach to assessment, the authors propose we can improve pain management for cancer patients.

Preamble Note:

Practice guidelines are intended to assist health care professionals with decisions throughout the spectrum of the cancer experience. This guideline is intended to assist health care professionals to care for cancer patients with pain. Management must be customized to meet the unique needs of individuals and their families. Information on pain management for children with cancer may be obtained from the IWK Health Centre Pain Team.

Guidelines should never replace specific decisions for individual patients, and do not substitute for the shared decisions between any patient and doctor (or other health professional) which are unique to each circumstance. Guidelines do provide evidence-based background information, consensus-based recommendations for similar problems, and a context for each individual decision.

This guideline will be reviewed in three years from publication date or earlier if important new evidence becomes available. Current versions of this guideline will be available on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca)

These guidelines are designed for health care professionals, working in a variety of settings. For front-line health care givers, the short version of the guidelines will be a useful reminder of assessment and treatment. This version will be useful for those who prefer to read a bit more about the recommendations. The full evidence-based discussions of these guidelines are located in the Appendices, available on request or at the *Cancer Care Nova Scotia* website. Development of these guidelines is described in Appendix II.

Patients, families and other non-health care professionals are recommended to review materials written for the lay public, such as the Living Well With Cancer information series.

Comment on Evidence:

There is a scarcity of clinical trial evidence on most aspects of cancer pain management. Randomized controlled trials represent only 1% of the published literature on cancer pain and have enrolled only 1 in 10,000 patients at risk for cancer pain[1]. The multidimensional nature of cancer pain creates difficulties in generating level I & II clinical research studies on specific treatment questions. When high-quality evidence was not available, a 'best practice' approach was used to develop this guideline. Clinicians must continue to provide the best possible care for cancer-related pain, despite the absence of definitive evidence. Best practices include experience and sound clinical judgment, aided by level III & IV evidence where available, and must be given serious consideration for patient care and policy decisions.

Comment on Clinical Research:

An important component of treatment decision-making for any patient is the potential for enrollment in relevant clinical research. The Supportive Care Cancer Site Team is committed to advancing patient care, through participation in clinical trials and other clinical research projects. At any point in time, there may be a clinical trial or other clinical research opportunity related to any component of this guideline. As specific trials or clinical research projects become available, eligible patients may be offered the opportunity to enroll in the relevant trial or research project. Every effort will be made to accommodate patients for clinical research participation, but there will be eligibility restrictions for each trial. Patients are encouraged to discuss clinical research opportunities with their health care providers. Other researchers may also contact patients to offer participation in relevant trials. Current clinical trials will be listed on the *Cancer Care Nova Scotia* website (www.cancercare.ns.ca)

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For further information on this, or any other Practice Guideline, please contact the CST Co-Chairs, or members of the Guidelines Resource Team, *Cancer Care Nova Scotia* (Tel. 1-866-599-2267 or by e-mail info@ccns.nshealth.ca)

Reference:

1. Goudas L, Carr DB, Bloch R, et al. Management of cancer pain. Evidence Report/Technology Assessment No. 35 (Prepared by the New England Medical Center Evidence-based Practice Center under Contract No 290-97-0019). AHRQ Publication No. 02-E002. Rockville, MD: Agency for Healthcare Research and Quality. October 2001.

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Part 1. Introduction

Cancer is leading cause of morbidity and mortality in our society, and most patients will experience pain at some time during their cancer experience. In Canada, it is estimated there are about 140,000 new cases and 67,400 deaths from cancer each year. Men outnumber women for both new cases and deaths (Figure 1.1). The numbers of new cases and deaths continue to rise steadily as the Canadian population increases and ages; these rising numbers are an important measure of cancer burden on the Canadian population[1].

By comparison, in Nova Scotia more than 22,000 people in Nova Scotia were diagnosed with invasive cancer between 1995-1999. On average, approximately 2,000 cases were registered annually for each gender[2].

The incidence of cancer in a population is an age and gender dependent phenomenon. More than two-thirds of all new cancer cases in Nova Scotians occur after the age of 60 years (Figure 1.2). The relative increase in incidence rates adjusted for age was much more pronounced for males than for females.

Pain is one of the most common symptoms associated with cancer, affecting about two thirds of patients overall. A considerable proportion of patients (15% to 25%) experience significant pain in association with early, localized, even curable disease. If pain is poorly controlled in a patient with cancer, it may reduce the patient's compliance with

New Cases and Age-Standardized Incidence Rates (ASIR) for All Cancers, Canada, 1975-2004

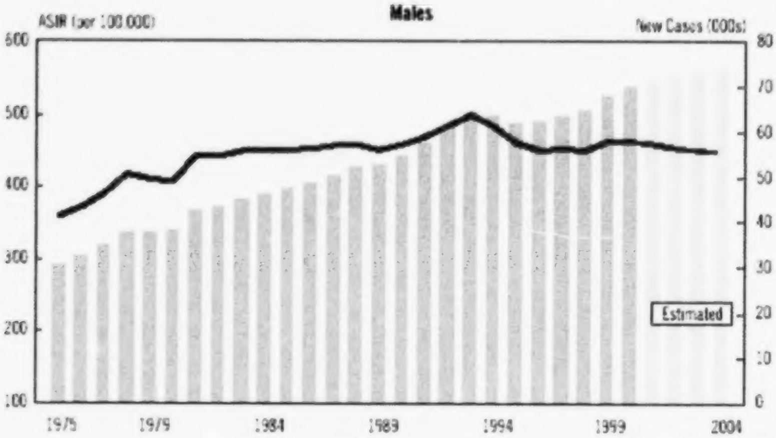
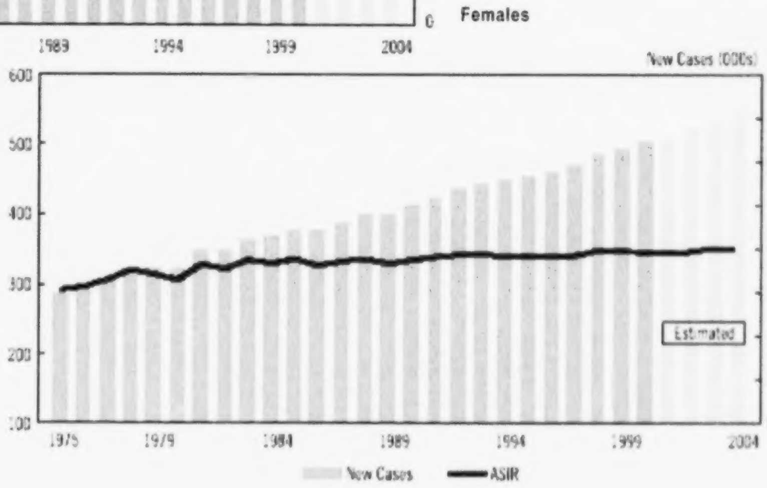


Figure 1.1 Canadian Cancer Incidence Rate by Gender[1]



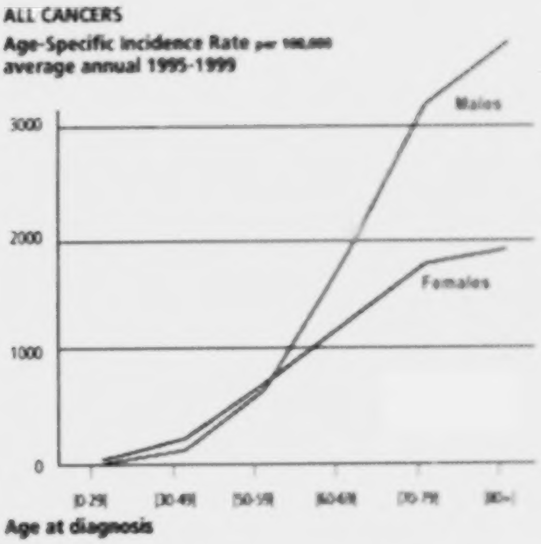
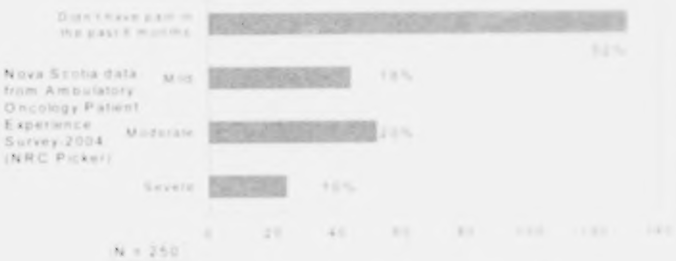


Figure 1.2. Age-specific incidence rate for all tumour sites combined, males and females, Nova Scotia 1995-1999[2].

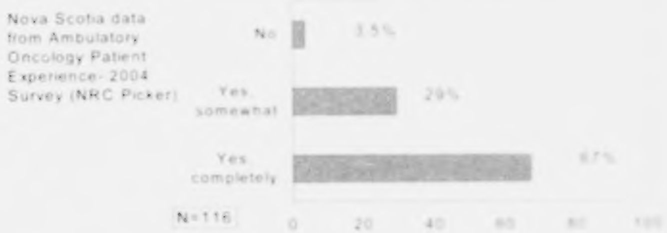
demanding cancer treatments. With the development of metastases, the incidence of pain increases to 40% to 60% of patients, and in far advanced disease, 60% to 90% of patients report significant pain[3,4]. Clearly, the increasing numbers of cancer patients and the proportion of cancer patients with pain combine to make cancer pain a significant public health problem.

Figure 1.3 In the past 6 months, if you had pain was it mild, moderate or severe?



Nova Scotia data from Ambulatory Oncology Patient Experience Survey-2004 (NRC Picker)

Figure 1.4 Do you think staff did everything they could to control your pain or discomfort?



Nova Scotia data from Ambulatory Oncology Patient Experience- 2004 Survey (NRC Picker)

1.1 Epidemiology

Cancer-related pain encompasses pain caused by cancer, by procedures used to treat cancer, and by the side effects of cancer treatment. The epidemiology of cancer-related pain has been analyzed by the Agency for Healthcare Research and Quality (AHRQ- formerly the Agency for Health Care Policy and Research, AHCPR).

The epidemiological findings of the AHRQ demonstrate that a substantial portion of the disease burden of cancer is related to pain. As the estimates are taken from patients diagnosed and treated for cancer in conventional medical settings, the disease burden of cancer pain may be underestimated. Patients who are not within the conventional medical system appear to be at greater risk for under-diagnosis and under-treatment of cancer and cancer-related pain. These patients may have chosen only to use complementary therapies exclusively[5], or they may be unable to afford prescription medications (or medical care in the USA), or they may live in rural or other underserviced areas.

In Nova Scotia, a survey (fall 2004) of patients at the two adult cancer centres illustrated that nearly half had experienced pain within the last six months, and 30% had moderate to severe pain (Figure 1.3). The survey results, of patients who had at least one active treatment visit within six months of receiving the survey, illustrated that 28% of patients who had experienced pain in the last six months felt that their health care provider did not do everything to help control pain and discomfort (Figure 1.4). These data suggest that cancer-related pain remains a significant problem among the cancer patient population.

A substantive proportion of the Nova Scotia population resides in rural communities, and may be limited in their access to specialized health care. Many cancer patients in Nova Scotia are uninsured or underinsured for prescription drugs and home medical supplies.

Risk factors such as belonging to a minority group, being female, or being elderly affect the adequacy of cancer pain assessment and treatment. There is a concern that people who receive minimal medical care (e.g. uninsured patients, regions with less medical service available) experience an even greater cancer pain burden. The World Health Organization has documented the widespread prevalence of inadequate cancer pain relief around the world, even in developed countries such as Canada.

Cancer mortality rates have declined slightly for males and remain fairly constant for females over the past 3 decades in Canada (Figure 1.1). Increasingly successful cancer treatment has improved survival. Long-term survivors may have persistent pain, which reduces functional status and quality of life.

Cancer treatment may lead to chronic pain. Chemotherapy or radiation therapy can induce painful neuropathies. Cancer surgery may produce chronic pain syndromes, but incidence estimates are difficult to derive with certainty. For example, about one quarter of women who undergo axillary dissection and either limited tumour resection or modified radical mastectomy experience postmastectomy chronic pain syndrome. Chronic postsurgical neuropathic pain has been described in the thorax or neck and visceral organs, such as the bladder. Phantom pain affects about a third of patients after limb amputation.

Cancer pain contributes substantially to the burden of the illness, yet there is inadequate information about the prevalence and incidence of this common phenomenon. More research is needed to fully understand the epidemiology of cancer pain.

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Part 2. Barriers to Pain Assessment and Management

Health care institutions and health care professionals have a responsibility to assess pain and provide pain management for cancer patients. It is estimated that about 85-90% of patients who experience pain could be managed with current knowledge and resources[1], but numerous studies indicated that only 20-50% of patients actually achieve adequate pain control[1-8]. Clearly, many patients with pain are not yet benefiting from the advances in pain management.

The barriers to pain management are numerous and complex, often poorly defined, and resistant to current efforts to change them. Three areas have been identified as significant barriers to pain management: the health care system (including regulatory restrictions), health care professionals, and patients and families[9].

2.1 Health care system

In the past pain was not recognized as a major management priority in the health care system. More recently, the Joint Committee on Accreditiation of Health Care Organization (JCAHO) has included pain as an auditable vital sign, for institutions in the US[10]. In Canada, the Canadian Council on Health System Accreditation (CCHSA), which sets national accreditation standards, is in process of addressing this issue.

If pain is recorded as a routine vital sign, it may be more visible to clinicians and may raise awareness of the problem[11]. Patients are likely to receive better pain relief if the health care system holds health care professionals responsible for assessing and relieving pain.

An important priority for health care system standards is to avoid unnecessary harm to patients. Generally, cancer pain has not been considered to be harmful, as it was not believed to shorten lifespan. It is now recognized that pain is harmful. Contrary to our cultural attitude of "no pain, no gain," pain can kill. Pain may inhibit the immune system and enhance tumour growth[12, 13].

Improved pain management is cost-effective. Studies have demonstrated that adequate pain management can result in a decrease in adverse effects, shorter hospital stays[14-18], and improved patient outcomes. Despite this evidence, resource allocation for pain management often remains a low priority. For example, specialized pain clinics and advanced pain management techniques are not readily available to cancer pain patients in Nova Scotia, due to long waiting periods inconsistent with the timecourse of cancer pain progression.

Another resource problem in Nova Scotia is prescription drug coverage. Publicly funded prescription insurance is available for very low-income families and seniors over 65 years old. Some seniors cannot afford the premium for the public plan. Further, an estimated 30% of the population does not have any insurance for prescription medications. Many of these uninsured or underinsured patients are unable to pay for pain relief medications (or other medications) and/or make choices not to purchase these medications. Often these patients require hospitalization to manage uncontrolled pain, at greater cost to the public and greater suffering to these patients.

2.2 Regulations

Since the early 20th century, federal legislation has been aimed at restriction and control of narcotics through strict law enforcement of both the public and health care professionals. Narcotic is a legal term to describe several drugs with abuse potential, and includes the pharmacologic drug class of opioids (drugs which act like morphine to reduce pain), as well as other drug classes (e.g. cannabinoids). Emphasis has been placed on illegal narcotic usage, rather than its legitimate medical uses. This emphasis continues to date[19].

Until the Controlled Drugs and Substances Act was passed in 1997, narcotics were controlled through regular inspections of pharmacy-controlled substance dispensing records and a national registry of all controlled substance prescriptions. Today, anyone can file a complaint with the provincial College of Physicians and Surgeons, which will result in a formal review of a physician's narcotic prescribing. This potential threat has a significant effect on the prescribing behavior of many physicians.

In Nova Scotia, narcotic prescriptions require the use of a triplicate prescription, with one copy filed in a central provincial registry for audit. While this requires substantive effort on the part of all parties and does reduce the number of narcotic prescriptions, it is not proven to reduce narcotic abuse. The requirements of this process are an operational barrier to timely prescribing of opioids for cancer patients, and the program reinforces prescriber behaviors to be very conservative in the use of opioids, even when they are clinically indicated. Similar programs in the United States, with strong law enforcement, have led to prescribing patterns with a strong avoidance of targeted opioid agents, and inappropriate use of non-opioids alone for management of severe cancer pain.

Methadone was originally developed in the 1930's as an opioid analgesic. Methadone is a synthetic agent, structurally unlike morphine, with prolonged analgesic effects and minimal euphoric effects. This agent was first authorized in Canada for the treatment of opioid addiction in the early 1960s, and is still controlled by restrictive federal regulations. Individual physicians are required to obtain federal authority to prescribe this drug. Methadone is an effective and inexpensive analgesic, but patient access is limited by this regulatory barrier.

2.3 Health Care Professionals

Health care professionals themselves may be barriers to effective pain management. Lack of education, fear of regulatory scrutiny, concerns about addiction and respiratory depression from opioids, and poor pain assessment and management skills are some of the contributing factors.

Knowledge and skills for pain assessment and management are often not included in training programs for health care professionals. Older curricula often included misleading or incorrect information. Evaluation of educational programs did not consider the need for inclusion or improvement of pain management training. The exclusion of pain management from initial training programs may have influenced health care professionals to perceive it as a low priority. In recent years, the trend has changed towards a greater emphasis on pain management skills in training curricula. Pain management is also being addressed in continuing education programs for practicing health care professionals[20]. Despite these recent advances, many health care professionals still lack sufficient education for effective pain management. Recent health care professional graduates often learn from experienced preceptors, who may not have been properly educated on current pain management concepts.

The literature on pain is abundant. Pain is now regarded as a science and as a field of specialization in health care. The knowledge and technology now available can provide safe and effective pain relief for most people who suffer pain. The first widely used clinical practice guideline was Cancer Pain Relief, published in 1986 by the World Health Organization (WHO)[21]. Many other organizations have subsequently published guidelines. Despite the growing magnitude of knowledge, this information has not been fully assimilated into clinical practice.

Furthermore, health care professionals are often not well trained in communication skills. The relationship established between health care professionals and patients and their families is crucial to effective pain management. Patient and family choices often depend upon information received from health care professionals. Poor communication can be an impediment to optimal patient care.

Health care professionals are trained to be objective in diagnosis, and to use biometric measurements. Pain, however, is a totally subjective experience, and is measured by psychometric scales. Subjective assessment techniques are used by some health professionals, but objective assessment of pain severity by health professionals has proven to be inaccurate in a number of studies[22-24]. Only the patient can identify and quantify their pain. Accepting and acting upon the patients' self-report of pain can be difficult for many health care professionals. This is another significant barrier to the effective management of pain.

Some patients are unable to report their pain, such as those who cannot communicate verbally. These patients are at risk of having their pain unrecognized and untreated. Another group of patients may lie to health professionals to obtain narcotic analgesics for illicit use. Other patients may exaggerate pain severity to compensate for chronic under-treatment of pain. Differentiating these can be challenging for health professionals and may lead to a behaviour of under-estimating pain severity and under-treating the pain[2].

For decades the dangers of opioid analgesics have received far more attention than their benefits. Opioids have a reputation for being very dangerous drugs that have the capacity to kill or change a person into a drug addict. Although there are risks associated with the use of opioids, there is evidence that health care professionals over-estimate the potential for drug addiction[25]. Several studies have shown that the actual risk is far less than 1%[26-28]. Health care professionals have difficulty understanding the difference between tolerance, physical dependence and addiction. These perceptions are an obstacle to the appropriate use of opioid analgesics for management of cancer pain.

The likelihood of respiratory depression is also over-estimated by health care professionals[29]. The low risk of respiratory depression in opioid-tolerant patients is poorly understood by health care professionals. In the rare instances where respiratory depression has occurred, it has been easily managed by well-known techniques.

Another problem is the concern by health care professionals that they may be harmed by people seeking drugs for abuse. Due to personal security concerns, some community pharmacies limit their stocks of narcotic agents and may not stock all strengths of each product. Patients often experience difficulties getting prescriptions filled, especially for large quantities of strong opioids. Physicians' offices may refuse to stock narcotic agents. Both physicians and nurses are reluctant to transport narcotics for use in the care of patients in the home. These practical barriers further limit the use of opioid agents for pain management.

2.4 Patients and Family

Barriers to effective pain assessment and management are present within the patients and families themselves. Patients often fear their pain and what it means, and they hold strong views on the use of opioid analgesics. If a patient refuses to take opioid analgesics as ordered by the physician, the medication cannot alleviate pain adequately (e.g. refusal to take opioid around the clock). Likewise, if a family member fears the opioid analgesics, they may influence the patient to limit or refuse pain medications.

Many patients believe that pain is a normal and inevitable part of cancer. Some feel that they should endure pain for as long as possible, before seeking help. Others may feel that if their pain is relieved they will not know if their cancer is progressing. Another common patient belief is that they should be 'good patients' and not bother their doctors (or other health caregivers, or families) with their pain problems. They will also put up with their pain for fear that they may distract their doctors from treating the cancer and other symptoms.

Patients from different cultures, religions or belief systems may have other views on pain than those of the caregivers. Some will accept pain with stoicism, while other may exaggerate their pain experience. Some cultures view pain and illness as punishment for past misdeeds or believe there is a redemptive value to pain and suffering. Gender and age may sometimes affect the expression of pain, which may be further influenced by the patient's culture. Patients may have had past experiences with pain, which influence how they cope with their current cancer pain.

Denial of disease or disease progression is a known coping strategy used by patients with cancer. Pain is a constant reminder of this disease. By refusing to admit to pain, the patient can deny that they have cancer.

Patients may also associate increasing pain with disease progression, and impending death, so they minimize or deny worsening pain. Others feel that by not admitting to pain, they may halt the disease. Some patients do not want to face the implications of disease progression and the possibility of death. They do not necessarily understand that pain may worsen with or without disease progression.

Some patients cope with cancer by seeking alternative therapies. By choosing these methods, patients may feel that they are using more natural healing or are maintaining hope when traditional medicine cannot cure their disease. Patients may refuse traditional medical care of their pain, in the hope that alternate therapies will be better. If the alternative option is not effective, these patients may be harmed.

Patients may associate eating and bowel regularity with their well-being. Some may have had difficulties with constipation. Patients are aware that many analgesics can cause or worsen constipation. Fear of constipation may be a barrier to narcotic analgesic use.

Many patients and families fear that opioids may cause sedation, fatigue, loss of mental control or hallucinations. There is also a worry that patients may lose their ability to drive or to interact with other people. They are concerned that they may become "too drugged".

Worse still is the fear of addiction from opioids. Patients and families mistakenly believe that any regular use of opioids will result in addiction. There is a strong stigma associated with addiction in our society. They do not want to be labelled as drug addicts. This is a major barrier for patients and families.

Patients and families are aware that pain may worsen during the course of cancer and that they may need narcotics for pain relief. Many view narcotics as a last resort or fear that if they start narcotics early in their disease, the drugs may not work later when they are 'really needed'. They believe that there is a maximum dose that can be taken. Patients are also concerned that tolerance will develop during treatment, and worry that they may end up taking 'more and more'.

Families and friends can influence patient decisions. Different perspectives on the goals of care may cause conflicts within families and with health care professionals. Cancer pain and its treatment can change roles and relationships within families, which may interfere with effective pain management. Burnout is a serious problem for family caregivers. Caring for cancer patients may also impose a significant financial burden on the patient and family, often beyond their expectations or means.

2.5 Summary

Barriers to effective pain management exist within the health care system, health care professionals, and patients & families. There may be other barriers to cancer pain management for individual patients. When planning patient care, it is important to understand these barriers, and to develop pain management strategies accordingly[30].

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Part 3. Basics of Pain in the Adult Cancer Patient

3.1 Definitions

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[1]. "Total pain is suffering related to and the result of the person's physical, psychological, spiritual, social, and practical state" [2].

These definitions describe pain as a phenomenon with multiple components that makes an impact on a person's psychosocial and physical functioning. They acknowledge the complexity of the pain experience. Pain is not determined by tissue damage alone. There is no predictable relationship between tissue injury and the sensation of pain. Patients may experience severe pain when there is no evidence of tissue damage. Sometimes, pain may be described as less severe than expected when patients are under stress or traumatized. The inability to identify tissue damage sufficient to explain the pain is not proof that the pain is of psychologic origin[3].

Because pain is a highly personal and subjective experience, a working clinical definition of pain should be **"Pain is whatever the experiencing person says it is, existing whenever he says it does"** [4]. **The patient's self-report of pain is the single most reliable indicator of pain**[5,6].

3.1 Pathophysiology

Understanding the concepts around the pathophysiology are important to management of cancer-related pain. A detailed discussion of pain mechanisms is described in Appendix I. Figure 3.1 illustrates a simplified pain pathway[7]. Many types of noxious stimuli may initiate the sensation of pain. The stimulus induces an action potential within the nerve, which is conducted along the nerve fibre to the dorsal horn of the spinal column. At this level, the stimulus may be subjected to both excitatory and inhibitory influences (gate control theory). When a sufficient level of excitation is attained, the action potential is conducted via ascending pathways to the brain, where the perception of pain occurs. This process is called **nociception**. Pain can be modulated within the brain and through descending pathways from the brainstem to the spinal cord. At each of these levels there are multiple neurotransmitters (i.e. chemical messengers), which effect the perception, intensity and duration of the pain experience. Therapeutic interventions are designed to modify the transmission or perception of pain.

Based on physiology, pain may be classified as either nociceptive (described above) or neuropathic (see Figure 3.1). Nociceptive and neuropathic pain differ from each other by their inferred mechanisms. Nociceptive pain is a result of an injury or insult to non-neurologic structures, and occurs in the presence of an intact nervous system. In contrast, neuropathic pain occurs as a consequence of neural injury and abnormal or pathologic transmission, processing, and integration.

3.2 Characteristics of Cancer Pain Based on Pathophysiology

Formulation of a pain diagnosis and treatment plan is dependant upon an understanding of the pathophysiology and clinical characteristics of the patient's pain (Table 3.2).

3.3 Classification

Given that pain is multidimensional and multifactorial, there are various methods to classify cancer pain. The various methods of classification are listed in Table 3.3. Some other special pain problems are discussed below.

FIGURE 3.1 - Inferred Pathophysiology of Cancer Pain

I. Nociceptive Pain A. Somatic Pain B. Visceral Pain	**II. Neuropathic Pain** A. Centrally Generated Pain B. Peripherally Generated Pain
I. Nociceptive Pain: Normal processing of stimuli that damages normal tissues or has the potential to do so if prolonged; usually responsive to nonopioids and/or opioids. A. Somatic Pain: Arises from bone, joint, muscle, skin, or connective tissue.. B. Visceral Pain: Arises from visceral organs, such as the GI tract and pancreas. This may be subdivided: 1. Tumour involvement of the organ capsule that causes aching and fairly well localized pain. 2. Obstruction of hollow viscus, which causes intermittent cramping and poorly localized pain.	**II. Neuropathic Pain:** Abnormal processing of sensory input by the peripheral or central nervous system; treatment usually includes adjuvant analgesics. A. Centrally Generated Pain 1. Deafferentation pain. Injury to either the peripheral or central nervous system. 2. Sympathetically maintained pain. Associated with dysregulation of the autonomic nervous system. Central Pain. Associated with damage to the brain, and altered sensory input. B. Peripherally Generated Pain 1. Painful polyneuropathies. Pain is felt along the distribution of many peripheral nerves. 2. Painful mononeuropathies. Usually associated with a known peripheral nerve injury, and pain is felt at least partly along the distribution of the damaged nerve.

Adapted from McCaffery M, Pasero C: *Pain: Clinical manual*, p. 19. Copyright © 1999, Mosby, Inc. Information from Max MB, Portenoy RK: Methodological challenges for clinical trials of cancer pain treatments. In Chapman CR, Foley KM, editors: *Current and emerging issues in cancer pain Research and practice* pp 283-299, New York, 1993, Raven Press; Portenoy RK: Neuropathic pain. In Portenoy RK, Kanner RM, editors: *Pain management- Theory and practice* pp 83-125, Philadelphia, 1996b, FA Davis.

3.4 Special Pain Problems

3.4.1 Chronic Non-malignant Pain in the Cancer Patient

Cancer patients may present with pre-existing chronic non-malignant pain, or may develop such pain during the course of their cancer. If chronic non-malignant pain and cancer pain co-exist, assessment and management of these patients may be more challenging[8].

3.4.2 Idiopathic or Psychogenic Pain

The reality of pain is sometime questioned by the observer (e.g. health care professionals, family members). Terms have been developed to express doubt in patient self-report of pain:

Supratentorial pain is a medical idiom expressing disbelief that the patient is experiencing physical pain.

Idiopathic pain has been defined as pain in the absence of any known pathology or other cause, or pain that exceeds the degree expected from the known organic pathology.

Psychogenic pain is pain that is a manifestation of a primary psychiatric disorder or is primarily influenced by psychological processes.

Pain is a subjective unpleasant sensation, experienced by the individual. Not all causes of pain are fully understood. The clinician needs to recognize the reality of the patient's pain, and act on the patient's self-report, even in the absence of a known physical cause. The presence of anxiety or depression should be carefully assessed. Interventions for underlying psychological distress or psychiatric disorders may be required concurrently with pain management.

3.4.3 Somatization

Somatization refers to pain based on psychosocial or spiritual suffering, but felt as physical pain projected on the body as a whole, or on a specific body part. Somatization may be suspected if:

- Significant psychosocial or spiritual issues are identified
- When there is no apparent physical cause for pain, but the patient describes pain as "all over"
- Pain appears to increase when alone, but improves with socialization, physical activity, or other distraction
- Escalating doses of opioids produce toxicity with little or no pain relief
- There is a history of abuse (sexual, physical, psychological)
- There is a family history of poor coping behaviors to long-standing illnesses

3.5 Prognosis

Uncomplicated nociceptive pain is the most common type of pain seen in cancer patients. It is also the type of pain most responsive to analgesics. About 75-80% of cancer patients have pain, which will respond to analgesics[9,10]. It is reasonable to expect good pain control in these patients.

Less commonly, patients present with pain which has limited or no response to analgesic treatment. It is important to assess all patients with cancer pain to identify prognostic factors, which may predict poor response to treatment. Poor prognostic factors are listed in Table 3.1.

Table 3.1 - Poor Prognostic Factors

- Neuropathic pain
- Incidental pain (pain severely exacerbated by an incident such as movement, coughing)
- Impaired cognitive functioning
- Major psychological distress
- Positive history of alcohol or substance abuse

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Table 3.2 - Pain Characteristics Based on Inferred Pathophysiology[11]

Nociceptive Pain		Neuropathic Pain	
Characteristics	*Examples*	*Characteristics*	*Examples*
A. Somatic Pain		***A. Centrally Generated Pain***	
• Constant or intermittent • Aching or throbbing in quality • Well localized	• Bone metastases • Tumour infiltration into muscle, soft tissue	Deafferentation pain: • Constant burning • Altered pain perception (dysesthesia, hypo/ hyperesthesia, allodynia) • Occasionally radiating	• Phantom pain • Post-herpetic pain
		Sympathetically-maintained: • Burning, lancinating, shooting, stabbing, electric shock-like pain • Temperature sensitivity	• Pain associated with reflex sympathetic dystrophy/ causalgia (complex regional pain syndrome, type I, type II).
		Central Pain: • Allodynia, hyperalgesia	• Post-stroke pain (early or delayed, superficial or deep) • Spinal cord injury
B. Visceral Pain		***B. Peripherally Generated Pain***	
• Constant • Aching, squeezing, cramping, colicky • Poorly localized, occasionally referred • Well localized when organ capsule involved	• Intra-abdominal metastases • Liver metastases	Painful neuropathies: • Weakness • Muscle cramping • Gnawing, diffuse • Continuous, deep burning, aching • Lancinating • Abnormal skin sensitivity (like sunburn)	Polyneuropathies • Diabetic neuropathy • Alcohol - nutritional neuropathy • Associated with Guillain-Barré syndrome
			Mononeuropathies: • Nerve root compression • Nerve entrapment • Trigeminal neuralgia

Definitions- Allodynia: Pain caused by a stimulus that does not normally provoke pain.
Hypoalgesia: Decreased pain sensation from a stimulus (e.g. numbness)
Hyperalgesia: Increased pain sensation from a stimulus

Table 3.3. Methods of Classifying Pain in Cancer Patients

Method	Example	Clinical Significance
Etiology	Tumour-related pain* (e.g., compression or ischemia of pain-sensitive structures)	Broadest of all classification schema. Determination of general etiology aids the clinician in formulating a rational treatment plan for cancer pain. It is important to understand that the management of cancer pain is not dependant on prognosis or disease stage.
	Treatment-related pain* (e.g., osteoradionecrosis, chemotherapy-induced neuropathy, postmastectomy syndrome)	
	Procedure-related pain* (e.g., venipuncture, lumbar puncture, bone marrow biopsy)	
	Debility and chronic illness* (e.g., muscle spasm from prolonged bed rest, decubitus ulcers)	
	Chronic non-malignant pain in cancer patients (e.g., low back pain, osteoarthritis) *See below*	
	Idiopathic or Psychogenic Pain *See below*	
	Somatization *See below*	
Pathophysiology	Somatic nociceptive*	By helping target the source of pain, more specific treatment may be offered (e.g., sympathetic block for visceral nociceptive pain). The presence of neuropathic pain, which is typically less opioid responsive than nociceptive pain, is an important feature because adjuvant analgesics (antidepressants, antiepileptic drugs, oral local anesthetics) may play a relatively more important role. See Table 3.2 **Inferred Pathophysiology Of Cancer Pain**
	Neuropathic*	
	Visceral nociceptive*	
	Mixed (nociceptive/neuropathic)	

Table 3.3. Methods of Classifying Pain in Cancer Patients (continued)

Method	Example	Clinical Significance
Chronicity	Acute	The rapidity with which pain needs to be treated may be based on the acuity of pain. Acute pain may require more prompt or aggressive treatment, directed at its source. Change in acuity may signal new underlying pathology. Patients with chronic pain may require additional interdisciplinary resources to help manage depression and suffering, and to facilitate rehabilitation.
	Chronic	
Severity or intensity	Mild, moderate, severe	Usual determinant of the potency of prescribed analgesic (NSAID for mild pain, "weak" opioid for moderate pain, "strong" opioid for severe pain). Regular measurement is required to gauge treatment outcome. See Part 4. **Assessment of Cancer-Related Pain**
	Visual Analogue Scale faces	
	0–10 numerical score	
Temporal features	Constant, intermittent, mixed, breakthrough pain	Helps determine optimal schedule for prescribing analgesic drugs (p.r.n. vs. around-the-clock, vs. around-the-clock + p.r.n.)
Patient characteristic	Anxiety, distant/recent history of alcohol or drug use, etc.	Individual characteristics may help determine need for patient-specific therapy.
Disease stage/ performance status	Early stage vs. advanced disease, curable vs. terminal disease, recurrent disease.	May suggest specific treatment options based on potential benefit/ burden, and may predict response to therapy. (ECOG = Eastern Co-operative Oncology Group)
	ECOG Performance Status	
Responsivity	Highly, moderately, or poorly responsive to treatment	Individual response to medications and other treatment modalities may vary.
Syndromal presentation	Plexopathy, cord compression, postsurgical syndromes, etc.	Awareness and early recognition of syndromes may guide pain management strategies. See Part 6.10 **Cancer-Related Pain Syndromes**

* See Appendix I for further discussion
NSAID = nonsteroidal anti-inflammatory drug; p.r.n. = as needed.

Part 4. Diagnosis & Assessment of Cancer-Related Pain

Guideline Recommendations: Assessment of Cancer-Related Pain in Adults

A specific objective for this guideline is t**o standardize the assessment of cancer-related pain in adults across Nova Scotia**. To achieve this objective, the following recommendations have been adapted from the "Guideline for the management of cancer pain in adults and children" by the American Pain Society[1].

1. A component of the initial assessment of each cancer patient should include screening questions to identify the existence of pain. Cancer patients should continue to be screened for pain at each visit with a health care professional. Inpatients should also be regularly screened for pain- once daily until it is established that pain is not a focus of care.
   (Grade A Recommendation)
2. If pain is identified as a focus of care from screening questions, health care professionals should perform a comprehensive pain assessment.
   (Grade A Recommendation)
   - Each patient's self-assessment should be used as the foundation for the assessment. For patients who are able and willing to complete a self-assessment questionnaire, the **Brief Pain Inventory** is recommended.
     (Consensus of Guideline Writing Team)
   - Health care professionals in all settings are recommended to their intial pain assessment on the **Pain Assessment and Care Plan.**
     (Consensus of Guideline Writing Team)
   - For the rating of pain intensity, the recommended standard is a 100mm vertical rating scale.
     (Grade B Recommendation)
   - For assessment of pain in special patient populations, including the very old, cognitively impaired patients, known or suspected substance abusers, and non-English-speaking persons an alternate strategy should be considered. An alternative pain rating scale recommended for self-assessment by these patients is the Faces Scale.
     (Grade A Recommendation)
3. The comprehensive pain assessment should include: the location(s), characteristic(s) and severity of all identified sources of pain; a detailed patient history to describe the presence of persistent and breakthrough pain(s) and the effect(s) of pain on function; an assessment of total pain aspects including a psychosocial assessment; a physical examination focussed on pain; and a diagnostic evaluation of signs and symptoms associated with common cancer pain presentations and syndromes.
   (Grade B Recommendation)
4. A valid pain assessment tool should be used to evaluate and document, at regular intervals, both pain intensity and the effectiveness of the pain management plan.
   (Grade A Recommendation)
   - The **Pain Management Flowsheet** is recommended for use in all settings where cancer pain is managed.
     (Consensus of Guideline Writing Team)
5. Patients and family caregivers should be taught how to complete a pain management diary in order to maintain the continuity of effective pain management across all settings.
   (Grade B Recommendation)
   - The **Patient Pain Control Diary** may be used for ongoing documentation by the ambulatory patient.
     (Consensus of Guideline Writing Team)
6. When a change occurs in the patient's pain or when a new pain occurs, a comprehensive pain assessment and diagnostic evaluation should be repeated (using the **Pain Assessment and Care Plan**), and the pain management plan modified as appropriate.
   (Grade B Recommendation)

7. Particular attention to the preferences and needs is required for patients whose education or cultural traditions may affect communication about pain, and for those patients who are cognitively impaired, non-English speaking, very old, known substance abusers or other special patient groups.
   (Grade B Recommendation)
8. The assessment for common cancer pain presentations and syndromes in the comprehensive assessment may minimize the morbidity associated with unrelieved pain through prompt diagnosis and treatment .
   (Grade B Recommendation)

See Table II-1 in Appendix II for Definitions of Evidence-Based Recommendations

4.1 Introduction

Pain is a complex multi-dimensional experience. The concept of total pain has been used to include physical, psychological, social, spiritual, practical and other components. Optimal assessment of these components of pain requires the skills of a team of health care professionals. Communication among team members is essential, and requires the use of common tools, which are both valid and practical. Common tools aid in coordination of the team members, and reduce duplication of efforts.

Pain assessment should include patient self-assessment (if possible), medical history and diagnostic information, physical examination, and psychosocial assessment. Certain pain syndromes may require a unique approach to assessment, and may need the involvement of an appropriate specialist. Pain changes over time, and on-going assessment is necessary[2].

Table 4.1 - Pain Screening Questionnaire

Include the following questions in each assessment of a cancer patient:

Do you have pain now?	Yes ☐	No ☐
Do you have any ongoing pain problems?	Yes ☐	No ☐
Are you taking any medications for pain relief?	Yes ☐	No ☐

If yes to any of the above:

Where is your pain?

How intense is your pain (on a scale of 0 = no pain to 10 = worst possible pain)?

Now: ☐ On average (usual): ☐

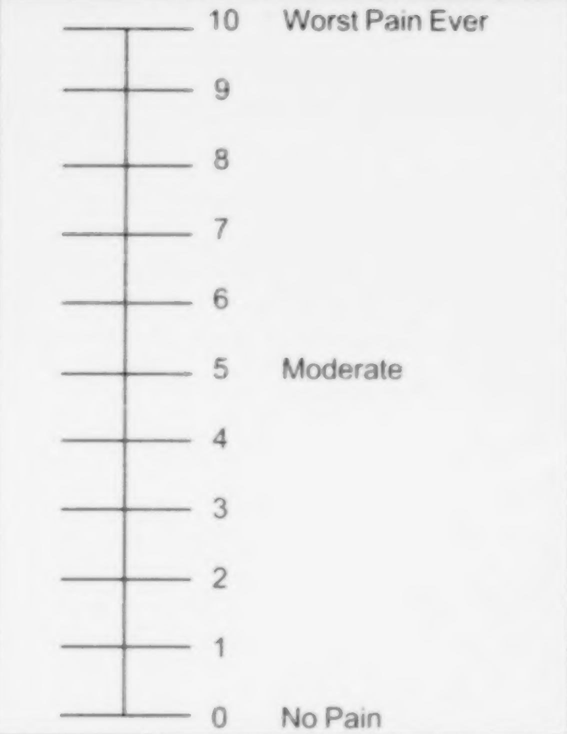
What medications do you take for pain relief?

What else are you doing to help with your pain?

Is your pain controlled to your satisfaction now?	Yes ☐	No ☐

If a pain problem is identified and is not under satisfactory control, complete the Initial Pain Assessment and Care Plan (Form 8.3) or refer to a pain management consultant.

Figure 4.1. Graphic Rating Scale for Pain Intensity Measurement

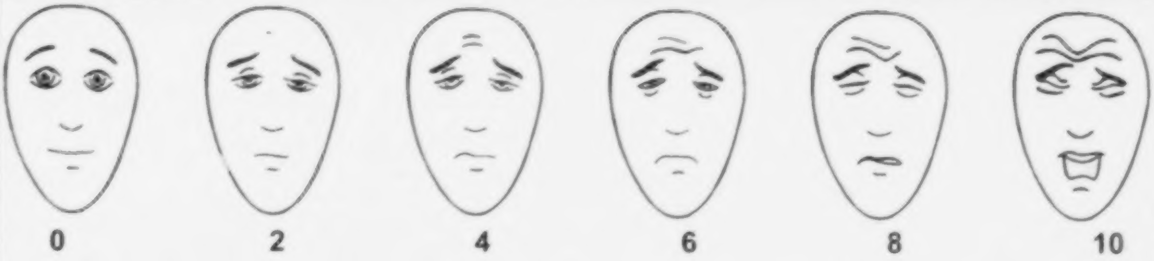


4.2 Pain Intensity Rating

A variety of measurement scales have been used for assessment of pain intensity. Scales which rate pain may be on a scale of 0 to 5 or 1 to 10[3], but the 0 to 10 scales have shown greater validity when compared to the 100mm visual analog scale (for continuous data)[4,5], and are easy to use by patients[6]. In addition, the numeric rating scales of 0 to 10 (a variation of the graphic rating scales used for subjective measurement of pain) are easier to use when the scale is vertical, like a thermometer[7,8]. For the rating of pain intensity in cancer patients, the recommended standard is a 100mm vertical line, with 10mm graduations and numeric values between 0 (at the bottom) and 10 (at the top) (illustrated in Figure 1). This scale is recommended for adult pain assessment tools.

For pediatric patients (and some adults), the graphic rating scale is not effective. The alternative pain rating scale recommended for self-assessment by

Figure 4. 2. Faces Scale for Pain Assessment in Pediatric Patients



In the following instructions, say "hurt" or "pain", which ever seems right for a particular child.

"These faces show how much something can hurt. This face *(point to left-most face)* **shows no pain. The faces show more and more pain** *(point to each from left to right)* **up to this one** *(point to right-most face)* **- it shows very much pain. Point to the face that shows how much you hurt** *(right now).*"

Score the chosen face **0, 2, 4, 6, 8** or **10**, counting left to right, so **'0'** = 'no pain' and **'10'** = 'very much pain.'

Do not use words like 'happy' and 'sad'. This scale is intended to measure how children feel inside, not how their face looks.

Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The faces Pain Scale - Revised: Toward a common metric in pediatric pain measurement. Pain 2001:93:173-183.

For correct administration and translations of the instructions, see www.painsourcebook.ca

Faces Pain Scale - Revised (FPS-R) From the Pediatric Pain Sourcebook. Original copyright c 2001.

Table 4.2 - Information to Include in a Pain Assessment

- Location of the pain (diffuse, point to location(s))
- Characteristics of the pain (descriptive words- e.g. burning, throbbing, sharp, aching)
- Timing of the pain (onset, duration, variation, pattern)
- Pain intensity (use 0 to 10 scale)
- Exacerbating and alleviating factors (what makes it better or worse)
- History of the pain, including response to medications (and adverse effects)
- Current pain medications, past pain medications (effectiveness)
- Associated symptoms (nausea, vomiting, constipation, sweating, tiredness)
- Cognitive impairment, memory deficits
- Current and past treatments for pain (PT, OT, chiropractic, acupuncture, heat, cold)
- Presence of psychosocial distress, other factors which affect 'total pain'
- Cultural, family, religious beliefs and practices which affect pain
- Social history (psychosocial impact of the pain on family, work, social life)
- Family History (mental illnesses, alcoholism)
- Results of physical exam
- Level of function; how does the pain impact (ADL, performance status of cancer, mood, sleep patterns, mental concentration)
- Fears, concerns about pain and medications; patient and family educational needs

these patients is the Faces Scale[9,10], as illustrated in Figure 2. Health care professionals may use this scale when a patient has difficulty understanding the numeric scale.

The purpose of measuring pain intensity is to provide a baseline for comparison with pain intensity ratings as the patient progresses and to determine the success of management strategies. If neither of the tools for rating intensity can be used by a patient, a different method should be found that the patient can use for comparison of their pain experience.

4.3 Initial Assessment & Diagnosis

The initial assessment of every cancer patient should include questions to identify the existence of pain. The questions which should be asked for cancer pain screening are included in Table 4.1. Cancer patients should continue to be screened for pain at each visit with a health care professional. Inpatients should also be regularly screened for pain- once daily until it is established that pain is not a focus of care.

If a pain problem is identified, and is not under adequate control, a detailed pain history should be taken and a physical examination should be performed. Some or all of the assessment should be delayed until the patient is able to complete it, if the patient is obviously in a lot of pain or is very fatigued. The patient should be referred to a pain management consultant, if necessary. Avoid duplication of the full workup and limit the initial assessment to data needed for a preliminary diagnosis, if a pain specialist visit is scheduled.

The detailed pain history is more than a routine medical history for a cancer patient. The pain history should include the information listed in Table 4.2.

For patients who are able and willing to complete a self-assessment questionnaire, the **Brief Pain Inventory** (Form 8.1- see Section 8) is recommended. It may be completed by patients or family members, and it may be repeated from time to time as necessary[9,11].

Health care professionals in all settings are recommended to complete an initial pain assessment[11] and to document this assessment on the **Pain Assessment and Care Plan** - Form 8.2 (see Section 8). It may be completed by one or more disciplines in the health care team. By using this form, it is

Table 4.3 - Examples for the Selection of Pain Assessment Tools

Tools Used by Patients and Family	Tools Used by Health Care Professionals

• Initial Assessment- **Brief Pain Inventory** (patient and/or family willing and able to complete)
• Ongoing assessment when pain is stable- **Pain Control Diary** or equivalent
• Periodic assesment, when pain is changing or more information is needed to inform health care professionals- **Brief Pain Inventory**
• Preference by patient and/or family- either **Brief Pain Inventory** or **Pain Control Diary** on a regular basis
	• Initial Assessment- **Pain Assessment and Care Plan** (multidisciplinary documentation, filed on Health Record)
	• Ongoing assessment - **Pain Flowsheet** or equivalent
	• Periodic re-assessment using the **Pain Assessment and Care Plan** may be necessary in situations such as:
	  • Pain is changing
	  • New symptoms are emerging
	  • Changes in patient information which could alter the care plan

expected that pain assessment and data collection will be systematic and comprehensive. Data gathered by each health care professional can be effectively communicated with each other. This form is to be part of the patient's health record. For consistency across Nova Scotia, the **Pain Assessment and Care Plan** is recommended as the standard for initial pain assessment in cancer patients.

4.4 Ongoing Assessment

As the care plan is developed, ongoing re-assessment is included in the plan. The ongoing assessment may be completed by the patient, the family, or the health care team. It is preferable for ongoing assessment to be completed directly by the patient, since pain is measured subjectively[2]. The **Patient Pain Control Diary** (Form 8.3- see Section 8) may be used for ongoing documentation by the ambulatory patient. Some patients prefer to keep a diary of their own design; for these patients, the clinicians should advise the patient which pieces of information need to be kept.

Re-assessment of cancer pain by health care professionals should be ongoing and should be documented on the patient's health record[6,12,13]. Documentation is a shared responsibility of all involved health care professionals. The **Pain Management Flowsheet** (Form 8.4- see Section 8) is recommended for use in all settings where cancer pain is managed- hospital inpatients, ambulatory clinic patients, long term care facilities, family doctor's office, or in the home. This **Flowsheet** should be used when **pain is a focus of care** (e.g. if the patient is not satisfied with the level of pain control). It should be kept in the patient's health care record for the setting where the pain is managed.

When pain is the focus of care for inpatients, this **Flowsheet** is recommended for routine documentation, every four hours or more frequently while pain is not controlled[14-16]. It may be kept at the bedside, and the patient may document their own intensity and satisfaction. Pain assessment should be done when a dose of analgesic is given, and considered when the peak of analgesic action is expected and/or when the analgesic dose duration is expected to end. The intensity should be scored with the 0 to 10 vertical scale (as reported by the patient).

If pain is **not** the focus of care (e.g. there is little or no pain, or the pain is well managed with analgesics), the pain intensity may be recorded along with other vital signs in the patient's health record, at each new nursing shift or when the patient reports any new pain problem.

Periodically, a more thorough re-assessment may be required, using the **Pain Assessment and Care Plan.** Table 4.3 provides some examples of when a complete reassessment may be needed.

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Part 5. Management of Cancer-Related Pain in Adults

5.1 Definitions[1]

Addiction: A pattern of compulsive drug use characterized by a continued craving for an opioid and the need to use the opioid for effects other than pain relief (usually euphoria).

Adjuvant analgesic: A drug that has a primary indication other than pain (e.g., antidepressant or anticonvulsant) but is also analgesic for some painful conditions.

Agonist-antagonist: A type of opioid (e.g., pentazocine, nalbuphine, butorphanol) that binds to the kappa opioid receptor site acting as an agonist (capable of producing analgesia) and simultaneously to the mu opioid receptor site acting as an antagonist (reversing agonist effects).

Allodynia: A nonpainful stimulus is felt as painful in spite of the tissues appearing normal; common in many neuropathic pain conditions.

Analgesic ceiling: A dose beyond which additional analgesia is not obtained.

Antagonist: Drug that competes with agonists for opioid receptor binding sites; can displace agonists, thereby inhibiting their action.

Breakthrough pain: Pain that increases above the pain addressed by the ongoing analgesics. Includes incident pain and end of dose failure.

Ceiling effect: A dose above which further dose increments produce no change in effect.

Crescendo pain: A period of rapid pain escalation often associated with increasing distress and functional impairment.

Deafferentation pain: Pain after injury to nerve root or peripheral nerve and inferred to have a predominating central mechanism. A nonspecific term.

Dysesthesia: An unpleasant abnormal sensation, including allodynia. Burning, electrical, tingling, hypersensitive to stimuli, may include area of sensory loss. Commonly described as pins and needles, such as a limb "falling asleep." Paresthesia, by comparison, is abnormal but not painful.

Hyperalgesia: An exaggerated pain response to a pain-causing stimulus

Lancinating: Stabbing, knifelike.

Medically ill patients: Patients with other debilitating pathologic condition/illness in addition to pain, as opposed to those who have only the symptom of pain and are otherwise healthy.

Mu agonist: A type of opioid, includes morphine and other opioids that relieve pain by binding to the mu receptor sites in the central nervous system. Used interchangeably with the terms full agonist, pure agonist, and morphine-like drug. In this document, opioid agonist is used in place of mu agonist.

Narcotic: Obsolete term used to refer to what is now called opioid. Current usage is primarily in a legal context to refer to a wide variety of substances of potential abuse.

Neuralgia: Pain in the distribution of a nerve (e.g., sciatica, trigeminal neuralgia). Often felt as an electrical shocklike pain.

Neuropathic pain: Pain initiated or caused by a primary lesion or dysfunction in the nervous system.

NMDA: *N*-Methyl-D-aspartate.

Nociceptor: A receptor preferentially sensitive to a noxious stimulus or to a stimulus that would be noxious if prolonged.

Nonopioid: Preferred to "nonnarcotic." Refers to acetaminophen and NSAIDs.

NSAID: An acronym for nonsteroidal anti-inflammatory drug.

Opioid: Preferred to "narcotic." Refers to codeine, morphine, and other natural, semisynthetic, and synthetic drugs that relieve pain by binding to multiple types of opioid receptors in the nervous system.

Opioid side effects: Common undesirable symptoms resulting from opioids. These side effects may be temporary or preventable. They usually respond to therapeutic management when they occur.

Opioid dose-sparing effect: The dose of opioid may be lowered when a nonopioid is added.

Opioid toxicities: Exaggerated responses to the known side effects of opioids. Opioid toxicity usually refers to neurological symptoms. These adverse effects are more difficult to prevent or manage.

Paresthesia: Abnormal anesthetic sensation, including sensations of numbness, prickling, tingling, and heightened sensitivity.
Paroxysmal: Sudden periodic attack or recurrence.
Physical dependence: Physical reliance on an opioid evidenced by withdrawal symptoms if the opioid is abruptly stopped or an antagonist is administered.
Polypharmacy: The use of multiple drugs at the same time for treatment of pain and/or other symptoms
Receptor: Molecular components of cellular structure which bind to free molecules (called ligands) and result in an action within the cell. Receptors and ligands bind in a 'lock-and-key' arrangement, with varying degrees of specificity and bonding strength (affinity).
Refractory: Resistant to ordinary treatment.
Tolerance: A process characterized by decreasing effects of a drug at its previous dose or the need for a higher dose of drug to maintain an effect.

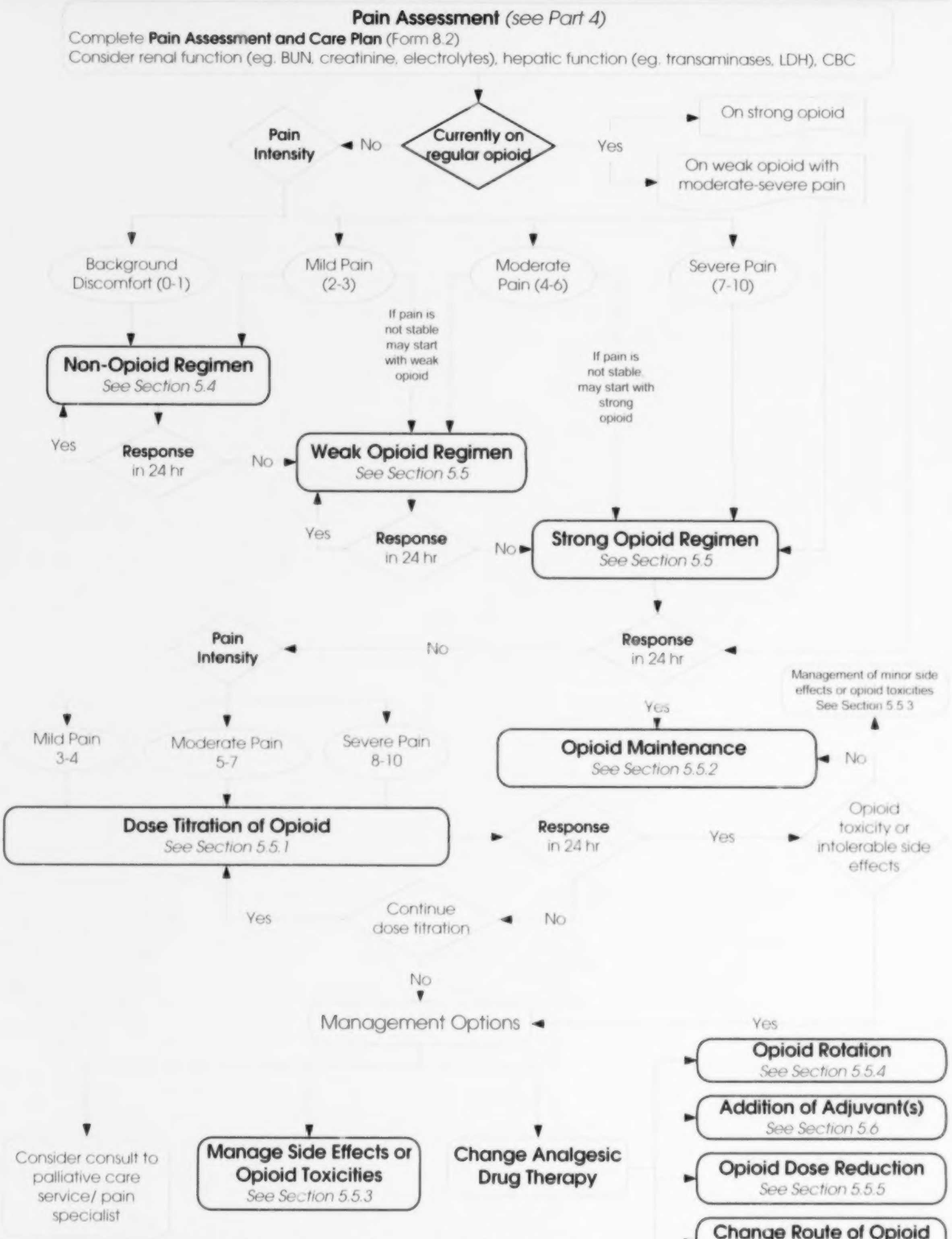
5.2 Principles of Treatment

Effective pharmacotherapy is the cornerstone of cancer pain management. Pain management also requires multiple non-pharmacologic approaches to address the various dimensions of total pain. Total pain may be different for each individual, but may include components of psychosocial or spiritual distress, history of pain in self or family which effects expectations, cognitive impairment, difficulties with social issues, communication or practical issues, impaired level of function, or other symptoms associated with the pain or its treatment. Any of these issues should be identified in the assessment and addressed individually as appropriate and as agreed with the patient.

The usual decision pathway for selection of initial pharmacotherapy, and ongoing management of drug therapy is illustrated in Figure 5.1. In simple terms, pharmacotherapy begins with a proper assessment of the patient and their pain (see Part 4). Based upon the intensity of the cancer pain, the initial drugs may be selected, starting with non-opioid agents for mild pain, 'weak' opioids for moderate pain, or 'strong' opioids for severe pain. This schema is often identified as the World Health Organization (WHO) Analgesic Ladder (Figure 5.2). The basic principles for the use of analgesic agents are outlined in Table 5.1.

Pain continues to be assessed as treatment continues. Generally, if the pain is adequately controlled, the medications are not changed. Strong opioids may be converted to controlled-release products for patient convenience, if the drug dosing is stable. If pain is not adequately controlled, the patient may be switched to more potent analgesics and/or the doses may be titrated to the desired response. Some patients may benefit from balanced analgesia, using more than one type of analgesic (an opioid and a non-opioid agent) concurrently, and minimizing the opioid dose. If the patient develops side effects or toxicity to the

Figure 5.1 Drug Treatment of Cancer -Related Pain


Pain Assessment *(see Part 4)*
Complete **Pain Assessment and Care Plan** (Form 8.2)
Consider renal function (eg. BUN, creatinine, electrolytes), hepatic function (eg. transaminases, LDH), CBC
Currently on regular opioid
No
Pain Intensity
Yes
On strong opioid
On weak opioid with moderate-severe pain
Background Discomfort (0-1)
Mild Pain (2-3)
Moderate Pain (4-6)
Severe Pain (7-10)
If pain is not stable may start with weak opioid
If pain is not stable, may start with strong opioid
Non-Opioid Regimen
See Section 5.4
Yes
Response in 24 hr
No
Weak Opioid Regimen
See Section 5.5
Yes
Response in 24 hr
No
Strong Opioid Regimen
See Section 5.5
Response in 24 hr
No
Pain Intensity
Yes
Management of minor side effects or opioid toxicities See Section 5.5.3
Mild Pain 3-4
Moderate Pain 5-7
Severe Pain 8-10
Opioid Maintenance
See Section 5.5.2
No
Dose Titration of Opioid
See Section 5.5.1
Response in 24 hr
Yes
Opioid toxicity or intolerable side effects
Yes
Continue dose titration
No
No
Management Options
Yes
Opioid Rotation
See Section 5.5.4
Addition of Adjuvant(s)
See Section 5.6
Opioid Dose Reduction
See Section 5.5.5
Change Route of Opioid
See Section 5.5.6
Consider consult to palliative care service/ pain specialist
Manage Side Effects or Opioid Toxicities
See Section 5.5.3
Change Analgesic Drug Therapy

May be duplicated for use in clinical practice. As appears in: Broadfield L, Banerjee S, Jewers H, Pollett AJ, Simpson J., Guidelines for the Management of Cancer-Related Pain in Adults. *© Cancer Care Nova Scotia*, 2005

Table 5.1 Principles of Use For Analgesics Agents[1]

Drug choice

- Determine the optimal type(s) of analgesic(s) (i.e. nonopioid, opioid, adjuvant) for the type and severity of pain, based on the Three Step Analgesic Ladder (Figure 5.2)
- Determine the long-range goals of pain management
  - Assess the effect of one analgesic before adding additional drugs
  - Mixed agonist-antagonist opioids should not be used for chronic treatment of cancer pain (e.g. pentazocine should not be used)
  - Certain opioids, such as meperidine or propoxyphene, should not be used for chronic treatment of cancer pain, due to adverse effects from cumulative dosing over time
- When opioids are used, provide a rescue dose for breakthrough pain (BTP)[6] (i.e. the oral opioid to be given every one or two hours as needed, or every 30 minutes for parenteral opioid- in addition to the around-the-clock (ATC)[7] analgesics)
  - The BTP drug should have a fairly rapid onset of action and short duration
  - The same opioid should be used for ATC and BTP doses, if possible; give 5-15% of 24-hour ATC dose (or 1/3 to 1/2 of the regular q4h dose) for each BTP dose; the BTP dose may be given as needed, ***including at the same time as the regular dose***

Route of administration

- The **oral route** is usually the **optimal route.**
- The subcutaneous (SC) or rectal routes may be used when the patient is unable to take oral medication. The SC or intravenous (IV) routes may be used when a quick onset of analgesia is desired.
  - If possible, the patient should be switched to equianalgesic doses by the oral route when pain control is stable.
- The IM route should be avoided, especially repeated IM administration
  - The IM route is painful and may cause fibrosis of muscle and soft tissue and sterile abscesses.

Dose

- Titrate dose of analgesic (opioid and nonopioid) to the desired pain relief effect.
  - Opioid doses must be titrated to optimize the balance between analgesia and side effects.
  - The nonopioids and adjuvants have a ceiling on their analgesia, but the opioids do not.
  - With opioids it is important to focus on the effect, not the number of milligrams. **No specific amount of opioid agonist is optimum or maximum.**
- For ongoing pain and breakthrough pain
  - Breakthrough doses may be given when needed, *including doses given at the same time as the scheduled ATC dose*
  - If > 3-4 breakthrough doses per 24 hours are needed, increase the ATC dose.
  - Titration of opioids for chronic severe cancer pain is usually done in 10% to 50% increments. If the previous opioid dose is safe but there is still pain, the opioid may be increased by 10% for mild residual pain up to 50-100% for severe residual pain.

Optimize administration

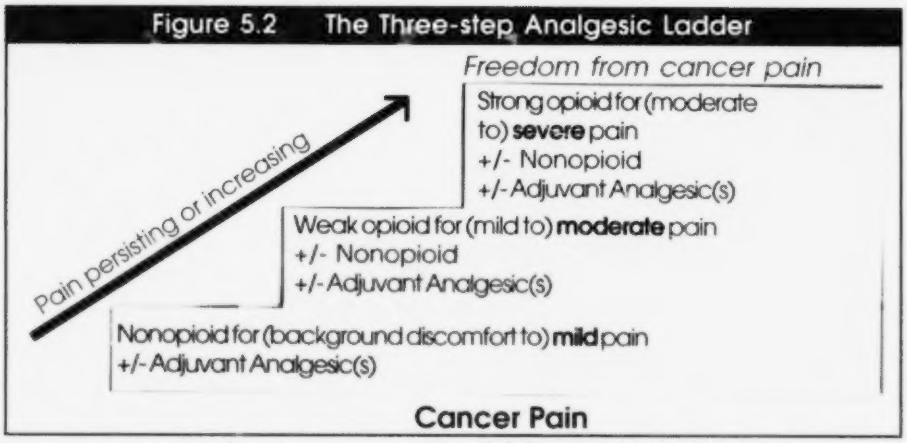
- Continue to monitor the pain and adjust opioids as needed to minimize pain. Educate the patient to ensure they know how to take their medications.
  - Analgesic agents should be given around-the-clock or ATC (regularly scheduled doses) if pain is present most of the day; if incident pain is predictable, give BTP analgesic(s) to prevent anticipated pain.

Ongoing pain

- It is easier to manage the pain than to repeatedly rescue the chronic pain. Pain assessment should be ongoing and doses titrated based upon assessment results (see Part 4)
  - Schedule analgesic doses to maintain a steady state of pain control (ATC dosing) with BTP rescue doses if needed, instead of PRN doses only.
  - Depending on the analgesic and whether it is a controlled release formulation, an ATC schedule may mean once daily (or BID) dosing or dosing every 4 hours or more often. Some NSAIDs and adjuvants require only one daily dose and some opioids with a short half-life are formulated in controlled-release tablets for once or twice a day dosing.
  - Intervals between doses should be individualized after observing the patient's response (for both short-acting and controlled-release analgesic drugs). e.g. opioids tend to have a longer duration of action in elderly patients, so dosing intervals should be no less than every 4 hours.

continued...

Figure 5.2 The Three-step Analgesic Ladder


Freedom from cancer pain
Strong opioid for (moderate to) **severe** pain
+/- Nonopioid
+/- Adjuvant Analgesic(s)
Weak opioid for (mild to) **moderate** pain
+/- Nonopioid
+/- Adjuvant Analgesic(s)
Nonopioid for (background discomfort to) **mild** pain
+/- Adjuvant Analgesic(s)
Pain persisting or increasing
Cancer Pain

opioid drug, an appropriate management option may be considered, including opioid rotation, changing the route of opioid administration, possibly opioid dose reduction, or the addition of adjuvant analgesic drugs. There may also be therapeutic approaches to directly manage the side effects or toxicities. It is important to individualize therapy to the needs of the patient, and, where appropriate, to consider mechanism-based approaches to the selection of treatment approaches (i.e. choosing the drug(s) or non-pharmacologic approach most likely to be effective based upon the biologic mechanism causing the side effect or toxicity).

The analgesic drugs will be discussed below in greater detail.

5.3 Pharmacologic Management- The Three-Step Ladder

The Three Step (WHO) Analgesic Ladder[2,3] (adapted in Figure 5.2) has been used for decades as a consistent approach for managing cancer-related pain. It focuses on selecting analgesics on the basis of the intensity of the pain using analgesics from each of the analgesic groups and building on previously effective analgesics, when appropriate[4,5]. The three steps of the analgesic ladder address different intensities of pain, however patients do not necessarily progress sequentially through each step of the ladder. Patients should be treated for their current severity of pain. The Analgesic Ladder also does not address types of cancer pain which respond better to certain adjuvant analgesics (non-opioids).

Steps 1, 2, and 3

Step 1 of the analgesic ladder addresses mild pain by recommending a nonopioid analgesic and the possibility of an adjuvant analgesic. The term adjuvant, when used in this ladder, refers to both the adjuvant analgesics and the adjuvant drugs that are

Table 5.1 Principles of Use For Analgesics Agents[1] (continued)

Pain management at end of life (final days of life)

- Pain is common at end of life, and sometimes pain may escalate rapidly
- Patients may be cognitively-impaired or unresponsive (particularly in the final days of life), but still have pain
- Continue with aggressive pain and symptom management. Opioid titratation is important with escalating pain. Education and involvement of the family is important.
- The oral administration of drugs may not be possible in final days; consider use of rectal, subcutaneous (SC), sublingual (SL) or transdermal route(s) for drug administration
- Monitor for symptoms of opioid toxicity as fluid intake declines and organ function diminishes
- Dosing and frequency of opioids may need to be adjusted

added to analgesics to reduce side effects (e.g., laxatives for opioid-induced constipation).

If pain is mild to moderate and not relieved by a nonopioid (with or without an adjuvant), step 2 recommends adding a 'weak' opioid[8]. The second step of analgesia builds on the previous analgesics, by adding an opioid to the previous nonopioid analgesic. The term 'weak' opioid is not accurate, but generally refers to an opioid with lower potency. Some 'weak' opioids have wide variations in oral absorption and hepatic metabolism to their active forms (e.g. codeine is inactive, but is metabolized to morphine). 'Weak' opioids may not be appropriate for severe, escalating pain, since the high doses needed may not be practical for administration. Often these opioid products are used in fixed-combination products with acetaminophen, for which dose-escalation may be limited by the nonopioid agent (i.e. the acetaminophen dose may only be escalated up to 4000 mg daily (12 tablets daily/325 mg acetaminophen per tablet), regardless of the opioid dose needed, due to hepatic toxicity).

Pharmacologically, no difference exists between 'weak' and 'strong' opioids. In clinical practice, the difference between steps 2 and 3 is choice of opioid analgesic and the use of combination products. If the pain is changing, it may be desirable to avoid step 2. This would avoid the need to change opioids or formulations as pain increases. Mild to moderate pain may be treated with low doses of plain oxycodone, morphine, or hydromorphone. These mu agonists may be continued through the course of therapy because doses of these may be escalated for the relief of increasingly severe pain. Opioid analgesics recommended at step 3 should be available orally and by a variety of other routes of administration so that the opioid need not be changed if the route of administration must change. Opioids used initially at step 3 also should have a short half-life so they can be titrated upward rapidly for severe, escalating pain. At the same time, for chronic pain it is advantageous if the short half-life opioid is available in a controlled-release formulation so that dosing intervals can be lengthened after the appropriate dose is determined with immediate-release formulations. Morphine and hydromorphone are favoured in step 3, due to the variety of routes and dosage forms available (including controlled-release preparations).

Other important recommendations that accompany the WHO analgesic ladder are to administer analgesics orally whenever possible and to administer them around-the-clock (ATC), to prevent the return of pain.

5.4 Non-opioids

The first step in the WHO Analgesic Ladder is mild pain, for which non-opioids are recommended. Some indications for the non-opioid analgesics are listed in Table 5.2. There are several non-opioid analgesics available in Canada. Most of these non-opioids are listed in Table 5.3.

5.4.1 Acetaminophen

Acetaminophen is a nonopioid analgesic[9] with fewer side effects than the non-steroidal anti-inflammatory drugs (NSAIDs). It has very little antiinflammatory effect. Acetaminophen does not affect platelet function, rarely causes gastrointestinal problems, and can be given to patients who are allergic to aspirin or other NSAIDs. Acetaminophen, however, may cause liver toxicity and should be used with caution in patients who regularly consume large amounts of alcohol or have pre-existing liver dysfunction[9-11]. The analgesic effect of acetaminophen has a ceiling, and the total daily dose is restricted. For adults, the usual recommendation is that the dose should not exceed 4000 mg/24 hr. It is available without a prescription. The mechanism of action for acetaminophen is not known, but appears to be different from aspirin and the other NSAIDs. Analgesia appears to result primarily from a central mechanism rather than a peripheral one[9,12].

Acetaminophen (and aspirin) are multipurpose analgesics, but their analgesic ability is frequently underestimated. As shown in Table 5.4, 650 mg of aspirin or acetaminophen may relieve as much pain as codeine 30-60 mg PO or oxycodone 3-5 mg PO.

5.4.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, relieve pain through multiple mechanisms, including a central nervous system (CNS) mechanism, and peripheral activity at the site of injury[1,13-18]. Tissue damage initiates a complex set of events leading to activation of primary afferent nociceptors and eventually to pain. NSAIDs relieve pain by interfering with the production of prostaglandins (PGs), which are produced through a series of events beginning when cells are traumatized and release phospholipids. The enzyme, phospholipase, breaks down phospholipids into arachidonic acid. The enzyme cyclooxygenase then breaks down arachidonic acid into PGs. NSAIDs block the action of cyclooxygenase, thereby interfering with the production of PGs and decreasing pain. Pharmacologically, NSAIDs are cyclooxygenase (COX) inhibitors. Dosing information on several NSAIDs is listed in Table 5.5.

NSAIDs reduce PGs throughout the body, and this may cause side effects[19-23]. Gastrointestinal erosion may occur when NSAIDs reduce the PGs which form the

Table 5.2
Indications For Nonopioid Analgesics

1. Mild pain. Start with a nonopioid. Acetaminophen or a NSAID alone often provides adequate relief.
2. Moderate to severe pain. Pain of any severity may be at least partially relieved by a nonopioid. For some types of moderate pain, especially muscle and joint pain, NSAIDs alone may provide adequate relief. However, a NSAID alone usually does not relieve severe pain.
3. Pain that requires an opioid. Whenever pain is severe enough to require an opioid, always consider adding a nonopioid for the following reasons:
   - Opioid dose-sparing effect (i.e., opioid dose may be lowered without decreasing pain relief. Reduces opioid-induced side effects).
   - Opioids and nonopioids relieve pain by different mechanisms.

Adapted from: McCaffery M, Pasero C: Pain: Clinical manual, p. 133. Copyright © 1999, Mosby, Inc.

Table 5.3 Non-Steroidal Anti-Inflammatory Drugs Available in Canada						
			Indication(s)			
Generic Name	Common Brand Name(s)	Generic Products	Pain	Arthritis	Inflammation	Dysmenorrhea
Acetaminophen	Tylenol	✓	✓			
Aspirin (ASA)	Aspirin, Entrophen	✓	✓	✓	✓	
Celecoxib	Celebrex		✓	✓		✓
Diclofenac	Voltaren	✓	✓	✓	✓	✓
Diflunisal	Dolobid	✓	✓	✓	✓	
Fenoprofen	Nalfon		✓	✓	✓	
Floctafenine	Idarac		✓		✓	
Flurbiprofen	Ansaid, Froben	✓		✓	✓	✓
Ibuprofen	Motrin, Advil	✓	✓	✓	✓	✓
Indomethacin	Indocid	✓		✓	✓	✓
Ketoprofen	Orudis	✓	✓	✓	✓	✓
Ketorolac	Toradol	✓	✓			
Mefenamic Acid	Ponstan	✓	✓		✓	✓
Meloxicam	Mobicox	✓		✓	✓	
Nabumetone	Relafen	✓		✓	✓	
Naproxen	Naprosyn	✓		✓	✓	✓
Oxaprozin	Daypro	✓	✓	✓	✓	
Piroxicam	Feldene	✓		✓	✓	✓
Sodium Salicylate	Dodd's Pills		✓	✓	✓	
Sulindac	Clinoral	✓		✓	✓	
Tenoxicam		✓		✓	✓	
Tiaprofenic Acid	Surgam	✓		✓	✓	
Tolmetin	Tolectin			✓	✓	✓

protective layer of the gastric mucosa. The common side effects from NSAIDs are described in Table 5.5.

In an effort to reduce side effects from NSAIDs, COX-2 specific NSAIDs have been developed. Most NSAIDs inhibit both cyclooxygenase 1 and 2 (COX-1 and COX-2) enzyme sub-types. COX-2 inhibition produces the analgesic and antiinflammatory effects of NSAIDs, whereas COX-1 inhibition causes many of the drug side effects, such as gastric ulcers. Newer NSAIDs, such as celecoxib, are more specific to COX-2 inhibition, but are not totally free from gastric ulceration as a side effect. Although the mechanisms of pain relief may differ between many of the NSAIDs, no well-controlled clinical trials demonstrate that combining one NSAID with another provides an analgesic effect superior to either one alone. Combining two NSAIDs increases risk of side effects and drug interactions. Adding aspirin to a NSAID may result in decreased or increased effect, but the result is not predictable. For these and other reasons, combinations of NSAIDs are not recommended (other than the low dose cardioprotective doses of aspirin).

NSAIDs were originally marketed for inflammatory conditions such as rheumatoid arthritis. This group of drugs are also useful as multipurpose analgesics, effective with postoperative pain, cancer pain, headache, menstrual cramps, and a variety of other painful conditions. Aspirin is

Table 5.4
Equianalgesic Chart: Approximate Equivalent Doses Of Nonopioids And Opioids For Mild To Moderate Pain

ANALGESIC	**PO DOSAGE** (mg)
Nonopioids	
Acetaminophen	650
Aspirin (ASA)	650
Choline salicylate	870
Magnesium salicylate, sodium salicylate	1000
Opioids	
Codeine	32-60
Hydrocodone	5
Oxycodone	3-5

Adapted from: McCaffery M, Pasero C: Pain: Clinical manual, p. 133. Copyright © 1999, Mosby, Inc.

TABLE 5.5 Acetaminophen and NSAIDS: Dosing Information

Chemical Class	Generic Name	Half-Life (hours)	Dosing Schedule	Starting Dose Oral (mg)	Maximum Oral Dose (mg/day)	Comments
P-Aminophenol derivatives	Acetaminophen	2	q4-6h	650	4000	Overdosage produces hepatic toxicity. No GI or platelet toxicity. Available as liquid and for rectal administration.
Salicylates	Aspirin (ASA)	3-12	q4-6h	650	6000	Standard for comparison. May not be as well tolerated as some of the newer NSAIDs. Available for rectal administration.
	Diflunisal	8-12	q12h	500	1500	Less GI toxicity than aspirin.
	Sodium salicylate	2-3	q4h	325	4000	Minimal GI toxicity. Minimal effect on platelet function.
Proprionic acids	Ibuprofen	2	q6h	400	3200	200mg & 400mg tablets are available OTC (no prescription needed).
	Naproxen	13	q6-8h	250	1250	
	Fenoprofen	2-3	q6-8h	200	3200	
	Ketoprofen	2-3	q6-8h	25	300	Available for rectal administration.
	Flurbiprofen	5-6	q12h	100	300	
	Oxaprozin	25	q24h	600	1800	
	Tiaprofenic Acid	4	q24h	600	600	
Acetic acids	Indomethacin	4-5	q8h	25	200	Higher incidence of GI and CNS side effects than proprionic acids. Available in slow-release and rectal preparations.
	Tolmetin	2-5	q8h	400	2000	
	Sulindac	16	q12h	150-200	400	Not recommended for prolonged use due to increased risk for GI toxicity.
	Diclofenac	2	q8h	25	150	
	Ketorolac	4-7	q6h	10	40	Use limited to 5 days. Recommended parenteral dose ≤30mg: total daily dose ≤120mg.
Oxicams	Piroxicam	50	q24h	20	20	
	Meloxicam	15-20	q24h	7.5	15	
	Tenoxicam	72	q24h	10-20	20	
Fenamates	Mefenamic acid	2	q6h	250	1000	Use limited to 7 days.
Other	Celecoxib	11	q12-24h	200	400	COX-2 specific NSAID. May reduce incidence of GI toxicity.
	Floctafenine	8	q6-8h	200-400	1200	Not recommended for long-term use.
	Nabumetone	24	q24h	1000	2000	Minimal effect on platelet aggregation.

Adapted from: McCaffery M, Pasero C: *Pain: Clinical manual*, pp.139-140, 1999, Mosby,Inc.

available without a prescription as are an increasing number of other NSAIDs such as ibuprofen and naproxen.

Choice of drug

- Whichever NSAID has worked well for the patient in the past and has caused minimal or no side effects is often the best place to begin with drug selection. Patients vary in response to NSAIDs. If one NSAID is ineffective after a few days of appropriate dosage adjustment, it is worthwhile to try another NSAID[24].
- If the patient is hypersensitive ("allergic") to aspirin or any other NSAID, all NSAIDs are contraindicated, but acetaminophen may be given[9,16]. Note that true allergy is sometimes confused with drug intolerance by patients. Gastrointestinal upset, for example, is not an allergic response and the patient may respond to an alternate NSAID without adverse effects.
- Acetaminophen is probably the safest nonopioid for most patients unless the patient has liver disease or a history of regular moderate to heavy alcohol intake (Table 5.6).
- When NSAIDs are used as a single dose at low doses or for only a short period of time (e.g., postoperatively), side effects are less problematic than with long-term use. Common side effects are described in Table 5.6, and drug-specific side effects are detailed in Table 5.7.
- For individual patients, the selection of an NSAID may be based upon the side effect profile and the drug-specific interaction of each agent (Table 5.8). The clinician should assess each patient for concurrent drug therapy and history of adverse effects from prior drug therapy, to help in the selection of which NSAID to select.
- Salicylate NSAIDs exhibit an adverse effect profile that is dose-dependant (Table 5.6). As the serum concentration increases with dose, the toxicities become increasingly severe. Salicylates are not often used for management of cancer-related pain.
- The risk of gastric ulcers from NSAIDs can be reduced by coadministration of misoprostol, a prostaglandin analog[19,24]. Unproven alternatives include giving an NSAID in combination with a proton pump inhibitor (e.g. omeprazole or pantoprazole), an H2 blocker (e.g. ranitidine or famotidine), sucralfate, and antacids[15,19,24].
- Most NSAIDs interfere with platelet aggregation. In patients with bleeding diatheses such as hemophilia and in some patients undergoing surgery or cancer treatment, it may be important to minimize increased bleeding[16,25]. Acetaminophen has no effect on platelet aggregation. NSAIDs that have minimal or no effect on platelet aggregation such as choline magnesium trisalicylate, and nabumetone, may be preferable when bleeding is a concern. None of these drugs has been proven safe in the setting of a bleeding diathesis.
- Nonprescription formulations are usually less expensive than prescription formulations. Acetaminophen, aspirin, and an increasing number of NSAIDs, such as ibuprofen and naproxen, are available over the counter.

Routes and dosing

- Acetaminophen and all NSAIDs are available orally. Only a few are commercially available for rectal administration, but most oral dose forms can be given rectally[26].
- Currently only ketorolac (Toradol) is available in adult doses for parenteral administration, IM or IV It is indicated for short-term use only.
- Acetaminophen and NSAIDs may be given as needed (PRN) for occasional pain or around-the-clock (ATC) for ongoing pain.
- Acetaminophen has a short half-life and usually must be given every 4 hours for ongoing pain.
- The half-lives of NSAIDs differ, and dosing intervals range from every 4 hours to once a day. For chronic pain, longer-acting NSAIDs which can be given once or twice a day are usually more convenient for patients and more likely to result in the patient taking all prescribed

doses. When patients are taking other analgesics or medications, consider selecting NSAIDs that allow for scheduling as many doses as possible at the same time. A ceiling or limit exists on the analgesia provided by acetaminophen and NSAIDs.

- For NSAIDs the ceiling dose for analgesia varies from one individual to another. If careful dose selection is desired, half the recommended dose may be given and then increased every few days until a further increase provides no additional pain relief or results in undesirable side effects. Then one may drop back to the previous dose. However, the dose should not exceed 200% of the recommended daily starting dose[23].
- For acetaminophen, potential hepatotoxicity limits the maximum dose to 4000 mg/day[27].
- Dosing of acetaminophen and NSAIDs is not affected by physical dependence and tolerance because these do not develop with repeated administration.

Table 5.6 Common Side Effects of Nonopioids and Their Treatment/ Prevention

Acetaminophen

Hepatotoxicity (nausea, vomiting, confusion, abdominal pain, followed by jaundice, and elevated bilirubin & liver enzymes) is more likely in patients with:

- Abnormal liver function tests
- Preexisting liver disease
- Regular use of alcohol
- Liver metastases, liver cancer
- Concomitant use of other potentially hepatotoxic drugs
- Older patients (> 60 years)

In these patients, reduce the total daily dose or avoid the use of acetaminophen

NSAIDs

1. Gastrointestinal side effects may include uncomfortable acute local irritation (e.g., heartburn, gastritis) or more serious gastroduodenal ulceration and perforation. The local irritation may be managed by:

- Taking the NSAID with food or a large glass of water.
- Lowering the NSAID dose.
- Switching to another NSAID.
- Using enteric-coated NSAIDs.
- Using an antacid or H_2 blocker (e.g., ranitidine) or proton pump inhibitor (e.g. omeprazole). (Note that antacids taken at the same time of day as the NSAID may reduce the NSAID absorption)
- Avoid concurrent use with steroids (e.g. dexamethasone)

Gastroduodenal ulceration and perforation may be prevented by:

- Selecting an NSAID with lower risk (e.g. ibuprofen, celecoxib).
- Using the lowest effective NSAID dose for the least period of time.
- Considering the prophylactic use of misoprostol as a gastroprotective therapy. Misoprostol is the only agent shown to reduce the occurrence of gastric and duodenal ulcers.

  Risk factors which warrant the use of gastroprotective therapies:
  - Prior ulcer disease
  - Concomitant corticosteroid or anticoagulant therapy

2. Hematologic abnormalities (e.g., bleeding, thrombocytopenia).

- Avoid the use of an NSAID.

3. Renal toxicity (e.g.edema, fluid retention, hypertension) is more likely in patients with renal dysfunction and/or dehydration. Preventive strategies in patients with impaired renal function:

- Use a lower daily doses of NSAID.
- Monitor kidney function.
- Stop use of the NSAID if renal function worsens.

4. Fluid retention, possibly with congestive heart failure

- Monitor edema and cardiac function closely

5. Cognitive dysfunction (CNS effect).

- Lower the dose.
- Discontinue the NSAID.

Salicylate Dose-Dependant Toxicities

Salicylate Concentration (mg/100mL)	Effect
19.5-21	Mild toxicity (tinnitis, decreased hearing)
25	Hepatotoxicity (abnormal liver function tests) Decreased renal function
30	Decreased prothrombin time
31	Deafness
35	Hyperventilation
>40	Metabolic acidosis, severe toxicity

Adapted from: McCaffery M, Pasero C: Pain: Clinical manual, p. 135. Copyright © 1999, Mosby, Inc.

Table 5.7 Specific Side Effects of Non-Steroidal Anti-Inflammatory Drugs (NSAID's)

A. Side Effects that Require Medical Attention	Acetaminophen	Aspirin (ASA)	Celecoxib	Diclofenac	Diflunisal	Fenoprofen	Floctafenine	Flurbiprofen	Ibuprofen	Indomethacin	Ketoprofen	Ketorolac	Mefenamic Acid	Meloxicam	Nabumetone	Naproxen	Oxaprozin	Piroxicam	Salsalate	Sodium Salicylate	Tenoxicam	Tiaprofenic Acid	Tolmetin
Allergic Effects																							
• Allergic dermatitis/skin rash	░	▨	▨	▨	■	■	▨	▨	■	□	▨	▨	░	□	■	■	■	▨	▨	■	▨	■	▨
• Anaphylaxis	□	░	░	░	░	░	░	░	░	░	░	░	░	░	□	░	░	░	░	░	░	░	░
• Hypersensitivity reactions	░	░	░	░	░	░	░	░	░	░	░	░	░	░	░	░	░	░	░	░	░	░	░
Cardiopulmonary																							
• Angina pectoris/chest pain	□	□	▨	▨	░	□	□	░	□	░	□	□	□	□	░	□	□	░	□	□	□	░	▨
• Cardiac arrythmias	□	□	□	▨	□	░	□	░	□	░	░	□	□	□	░	□	□	░	□	░	□	□	□
• Congestive heart failure	□	□	□	░	□	□	□	░	□	░	□	□	□	□	□	░	□	░	□	░	□	□	░
• Pulmonary edema	□	□	□	□	□	░	□	□	□	░	□	□	░	□	□	□	□	□	□	□	□	□	□
• Hypertension	□	□	▨	░	□	□	□	░	░	□	□	▨	□	□	░	□	░	░	□	░	░	□	■
• Hemoptysis	□	□	□	░	□	□	□	░	░	░	░	□	□	□	□	□	□	░	□	░	░	▨	□
Central Nervous System																							
• Confusion	□	□	□	░	□	▨	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
• Headaches (severe)	□	□	■	□	□	□	□	□	□	■	□	□	□	□	□	□	□	□	□	□	□	□	□
• Mood/mental changes	□	□	□	░	□	□	□	▨	□	▨	▨	□	□	□	□	□	▨	□	□	□	□	▨	▨
Digestive System																							
• Colitis	□	□	□	░	□	□	□	□	□	░	□	□	░	□	□	░	□	□	□	□	□	░	□
• Gastritis	□	□	□	□	□	□	□	□	□	□	□	□	□	□	▨	□	□	□	□	□	□	□	▨
• Gastrointestinal bleeding/ ulcerations	□	▨	□	▨	□	□	■	▨	□	□	□	□	□	□	□	□	□	□	□	□	□	□	▨
Genitourinary Effects																							
• Hematuria	□	□	□	□	□	□	■	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
• Cystitis, UTI's	□	□	□	□	□	□	■	■	□	□	▨	□	□	□	□	□	□	□	□	□	□	□	▨
• Dysuria	□	□	□	□	□	▨	■	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Hematologic Effects																							
• Agranulocytosis/granulocytopenia	░	□	□	░	□	░	□	□	□	□	□	□	░	□	□	□	□	□	□	□	□	□	□
• Anemia	░	□	░	□	□	□	□	□	□	□	□	□	▨	□	□	□	□	▨	□	□	□	□	▨
• Hemolytic anemia	□	░	□	□	□	░	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
• Leukopenia	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	▨	□	□	□	□	□
• Thrombocytopenia	░	□	□	░	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Hepatic Effects																							
• Hepatitis	░	□	□	░	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Otic Effects																							
• Change/loss of hearing	□	▨	□	□	□	▨	□	□	□	□	□	□	□	□	□	□	□	□	▨	□	□	□	□
• Tinnitis	□	▨	□	▨	▨	▨	▨	▨	▨	▨	▨	□	□	□	■	■	□	▨	▨	▨	□	□	▨
Renal Effects																							
• Fluid retention/edema	□	□	□	■	□	■	□	■	▨	■	■	■	□	□	■	■	□	▨	□	▨	▨	▨	■
• Interstitial nephritis	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
• Renal failure	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□

LEGEND:
■ More Frequent (3-9%) ▨ Less Frequent (1-3%) ░ Rare (<1%) □ Unknown

Continued...

Table 5.7 Specific Side Effects of Non-Steroidal Anti-Inflammatory Drugs (continued)

B. Side effects that only require medical attention if bothersome	Acetaminophen	Aspirin (ASA)	Celecoxib	Diclofenac	Diflunisal	Fenoprofen	Floctafenine	Flurbiprofen	Ibuprofen	Indomethacin	Ketoprofen	Ketorolac	Mefenamic Acid	Meloxicam	Nabumetone	Naproxen	Oxaprozin	Piroxicam	Sodium Salicylate	Sulindac	Tenoxicam	Tiaprofenic Acid	Tolmetin
Cardiovascular																							
• Tachycardia	□	□	□	░	□	▨	▨	▨	░	░	░	□	□	□	□	□	□	□	□	□	░	□	□
• Pounding heartbeat	□	□	▨	░	░	■	□	░	░	░	░	□	░	□	░	░	▨	□	□	░	░	░	□
• Flushing or hot flashes	□	□	▨	░	□	□	▨	▨	░	░	░	□	□	□	□	□	□	□	□	□	░	▨	□
• Increased sweating	□	□	▨	░	░	▨	▨	░	□	▨	▨	▨	□	□	▨	▨	□	░	░	□	░	□	□
Central Nervous System																							
• Dizziness	□	□	▨	▨	▨	■	■	▨	■	■	▨	■	■	□	■	■	□	▨	□	■	■	■	■
• Drowsiness	□	□	▨	□	▨	■	■	▨	□	▨	▨	■	□	▨	▨	■	▨	▨	□	□	□	▨	▨
• Headache (mild-moderate)	□	□	■	■	■	■	■	■	▨	■	■	■	□	□	■	■	□	▨	□	▨	■	■	■
• Nervousness, irritability	□	□	▨	□	□	■	■	▨	▨	□	■	□	□	▨	▨	□	□	□	□	▨	□	□	□
• Trembling or twitching	□	□	□	□	□	▨	□	▨	□	□	□	□	□	□	□	□	□	□	□	□	□	▨	□
• Trouble sleeping	□	□	■	□	▨	▨	■	▨	□	□	▨	□	□	□	▨	□	▨	□	□	□	□	□	▨
• Unusual weakness	□	□	▨	□	▨	■	▨	▨	□	□	□	□	□	□	□	□	□	□	□	□	□	□	▨
Gastrointestinal Effects																							
• Abdominal cramps, pain	□	□	□	■	■	▨	■	■	■	■	■	■	■	▨	■	■	▨	■	□	■	□	■	■
• Bloating, flatulence	□	□	■	▨	▨	▨	▨	▨	▨	□	■	▨	▨	■	■	□	▨	▨	□	▨	▨	▨	■
• Constipation	□	□	▨	■	▨	■	■	▨	▨	▨	■	▨	▨	▨	■	■	■	▨	□	■	▨	▨	▨
• Decreased appetite	□	□	▨	□	□	▨	▨	▨	▨	□	▨	□	□	□	□	□	▨	▨	□	▨	□	□	□
• Diarrhea	□	□	■	■	■	▨	■	■	▨	▨	■	■	■	■	■	▨	■	▨	□	■	▨	▨	■
• Epigastric pain, heartburn	□	■	■	□	□	□	□	□	■	□	□	□	▨	■	□	■	□	■	▨	□	▨	■	□
• Indigestion	□	■	□	■	■	■	■	■	▨	■	■	■	▨	▨	■	▨	■	▨	▨	■	■	■	■
• Nausea	□	■	■	■	■	■	■	■	■	■	■	■	■	□	■	■	■	■	▨	■	▨	■	■
• Stomatitis	□	□	□	□	▨	▨	▨	□	□	□	□	□	□	□	▨	□	□	□	□	□	□	▨	□
• Change in taste, dry mouth	□	□	▨	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□

LEGEND:

■ More Frequent (3-9%) ▨ Less Frequent (1-3%)

░ Rare (<1%) □ Unknown

Tables 5.7 & 5.8 adapted from:
Drug Information for the Health Care Professional, 24th Edition (USP DI 2004 Volume 1). Thomson Micromedex, Greenwood Village CO, 2004
and
Compendium of Pharmaceuticals and Specialties; The Canadian drug reference for health professionals. Canadian Pharmacists Association, Ottawa, 2004

Notes (Table 5.8):

1. Nephrotoxic medications- acyclovir, aminoglycosides, amphotericin B, biphosphonates, capreomycin, ciprofloxacin, cotrimoxazole, cyclosporine, foscarnet, gallium nitrate, gold compounds, lithium, neomycin, pentamidine, several chemotherapy agents, sulfonamides, tetracyclines, tretinoin
2. Hepatotoxic medications- alcohol, amidarone, androgens, ACE inhibitors, anticonvulsants, cotrimoxazole, erythromycins, estrogens, fluconazole, gold compounds, HMG-CoA reductase inhibitors, ketoconazole, methyldopa, niacin (dose) phenothiazines, retinoids, sulfonamides, several chemotherapy agents
3. Ototoxic medications- aminoglycosides, bumetanide, carboplatin, chloroquine, cisplatin, ethacrynic acid, furosemide, quinidine, quinine
4. Platelet aggregation inhibitors- alprostadil, anagrelide, dipyridamole, divalproate, pentoxifylline, sulfinpyrazone, valproic acid
5. Urinary acidifiers- ammonium chloride, ascorbic acid, potassium/sodium phosphates)
6. Urinary alkalinizers- carbonic anhydrase inhibitors, sodium bicarbonate

Table 5.8 Drug Interations with Non-Steroidal Anti-Inflammatory Drugs

	Acetaminophen	Aspirin (ASA)	Celecoxib	Diclofenac	Diflunisal	Fenoprofen	Floctafenine	Flurbiprofen	Ibuprofen	Indomethacin	Ketoprofen	Ketorolac	Mefenamic Acid	Meloxicam	Nabumetone	Naproxen	Oxaprozin	Piroxicam	Sodium Salicylate	Sulindac	Tenoxicam	Tiaprofenic Acid	Tolmetin
• Acetaminophen (↑adverse renal effects)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Alcohol, colchicine, corticosteroids, potassium supplements (↑gastrointestinal side effects)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Aminoglycosides										✓													
• Antacids		✓	✓	✓	✓	✓													✓	✓			
• Anticoagulants, heparin, thrombolytic agents, valproic acid (inhibition of platelet aggregation, bleeding)	✓	✓	(✓)	✓	(✓)	(✓)	✓	✓	✓	✓	✓	✓	(✓)	✓	(✓)	✓	✓	✓	✓	✓	✓	✓	✓
• Anticonvulsants (esp. phenytoin)		✓			✓														✓				
• Antidiabetic agents, insulin (↑hypoglycemic effect)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Antihypertensives, diuretics (esp. triamterene) (↓antihypertensive effect)		✓	✓	(✓)	✓	(✓)	(✓)	✓	✓	✓	(✓)	(✓)	(✓)	(✓)	(✓)	✓	✓	✓	✓	(✓)	(✓)	(✓)	(✓)
• Cholestyramine																					✓		
• Cyclosporin, gold compounds, nephrotoxic medications[1] (↑cyclosporin levels, ↑nephrotoxicity)			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
• Dimethyl sulfoxice (DMSO)																				✓			
• Digitalis glycosides (↑digoxin serum concentration)				✓	(✓)	(✓)	(✓)	⊖	✓	(✓)	⊖	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	⊖	(✓)	(✓)	⊖	(✓)	(✓)
• Hepatotoxic medications[2] (↑hepatotoxicity)	✓																						
• Laxatives (cellulose-containing)		✓			✓														✓				
• Lithium (↑lithium serum levels)			✓	✓					✓	✓						✓		✓					
• Methotrexate (↑bone marrow depression)		✓		✓	✓	✓	✓	✓	✓	✓✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Other non-steroidal anti-inflammatory drugs or salicylates (given concurrently)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Ototoxic medications[3]		✓			✓														✓				
• Platelet aggregation inhibitors[4] (↑bleeding)		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Phenobarbital						✓																	
• Probenicid		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Urinary acidifiers[5]		✓			✓														✓				
• Urinary alkalinizers[6]		✓			✓														✓				
• Zidovudine		✓			✓					✓									✓				

LEGEND:

✓✓ Serious/lethal interaction ✓ Known interaction (✓) Suspected interaction ⊖ No interaction

Notes- see page 33

5.5 Opioids

Opioids (sometimes incorrectly labeled as narcotics) are the mainstay drugs for the treatment of cancer pain. The prototype opioid drug is morphine. In recent years, we have begun to understand how and why opioids work to relieve pain.

Underlying Mechanisms of Opioid Analgesia and Side Effects

The natural physiologic system for modulating pain is based upon peptide neurotransmitters (3 families- enkephalins, dynorphins, and δ-endorphins) interacting at specialized receptors on nerve cells[28,29]. It is believed that the endogenous pain modulating system is associated with regulation of homeostasis and stress response. Opioids appear to interact with these receptors also, resulting in the analgesic and other pharmacologic effects from opioid drugs.

Opioid receptors are located in the CNS, pituitary gland, and the GI tract. They are particularly abundant in the periacqueductal gray (PAG) and dorsal horn of the spinal cord. Nociceptors carrying information about noxious stimuli from the periphery terminate in the dorsal horn of the spinal cord. These cells release neurotransmitters, such as adenosine triphosphate, glutamate, and substance P. It is at this site that opioids play an important role in pain control by locking onto opioid receptors and blocking the release of neurotransmitters, principally substance P.

There are three types of opioid receptor sites involved in analgesia: mu, delta, and kappa- see Table 5.9. When an opioid agonist binds to any of these receptor sites, it produces analgesia. Antagonists are drugs that also bind to opioid receptors but produce no analgesia. If an antagonist is present, it competes with opioid molecules for binding sites on the receptors. When a drug binds to any of the opioid receptor sites as an antagonist, analgesia and other effects from the opioid agonist are blocked[28-30].

TABLE 5.9 Summary of Actions at Opioid Receptor Sites

OPIOID RECEPTOR SITE	ACTIVITY	OPIOIDS WITH AGONIST ACTION	OPIOIDS WITH ANTAGONIST ACTION
Mu	Spinal and supraspinal analgesia, respiratory depression, cardiovascular effects, physical dependence, tolerance, decreased GI motility, urinary retention, pruritis, euphoria	**Pure:** e.g., morphine, methadone, codeine, fentanyl, sufentanil, alfentanil, oxycodone, levorphanol, oxymorphone, hydromorphone, meperidine	**Pure:** naloxone, naltrexone, nalmefene, butorphanol, nalbuphine, pentazocine, dezocine **Partial:** buprenorphine
Kappa	Spinal and supraspinal analgesia, miosis, psychotomimetic effects (dysphoria, agitation), and sedation without pronounced respiratory depression, euphoria, or GI effects	Butorphanol, nalbuphine, pentazocine, buprenorphine, sufentanil (weak affinity)	**Pure:** naloxone, naltrexone, nalmefene
Delta	Spinal and supraspinal analgesia without respiratory compromise. (Effects are under investigation)	Levorphanol, dezocine, sufentanil (weak affinity), morphine (weak affinity)	Naloxone, naltrexone, nalmefene, pentazocine

GI, gastrointestinal.

The effects (activity) a drug produces depends on the type(s) of opioid receptor(s) to which the drug binds and whether the drug acts as an agonist or an antagonist at that opioid receptor type. When a drug binds to any of these receptor sites as an agonist, it produces analgesia and other effects. When a drug binds to any of the opioid receptor sites as an antagonist, analgesia and other effects are blocked. Table 6.2 summarizes the activity of drugs when they bind to any of three opioid receptor types that are involved in analgesia.

Adapted from McCaffery M, Pasero C: Pain: Clinical manual, p. 167. Copyright @ 1999, Mosby, Inc.

TABLE 5.10 Characteristics of Selected Opioid Agonist Drugs

Opioid Agonist Drug	Routes Administered	Comments
Morphine	PO (IR and CR), PR, SL, IV, IM, SC, EA, IA	Standard for comparison. Multiple routes of administration. Controlled-release formulations available, but they are not therapeutically equivalent. Begin with lower doses in elderly. Active metabolite M6G can accumulate with repeated dosing in renal failure (may need to switch to a different opioid, such as hydromorphone).
Codeine	PO, IM, SC	IM has unpredictable absorption and high side effect profile; used orally for mild to moderate pain. Usually compounded with nonopioid (e.g.,Tylenol No. 3).
Fentanyl (Duragesic, Actiq)	OTFC, IV, IM, TD, EA, IA	Fast-acting; short half-life. At steady state, slow elimination from tissues can lead to a prolonged half-life (up to 12 h). On the basis of clinical experience, fentanyl, 1 mcg/h transdermally, is roughly equivalent to morphine, 2 mg/24 h orally, and fentanyl, 100 mcg/h parenterally and transdermally, is roughly equivalent to 4 mg/h morphine parenterally. Opioid-naive patients should be started on no more than 25 mcg/h transdermally. Transdermal fentanyl not recommended for acute pain management. Oral transmucosal fentanyl citrate (OTFC) is useful for management of breakthrough pain.
Hydromorphone (Dilaudid)	PO(IR and CR), PR, IV, IM, SC, EA, IA	Useful alternative to morphine. Controlled-release formulation available. No evidence that active metabolites are clinically relevant. Available in high-potency parenteral formulation (10 mg/mL) useful for SC infusion
Levorphanol (Levo-Dromoran)	PO, IV, IM, SC	Long half-life can lead to accumulation within 2-3 days of repetitive dosing.
Meperidine (Demerol)	PO, IV, IM, SC, EA, IA	No longer preferred for the management of acute or chronic pain because of potential toxicity from accumulation of metabolite, normeperidine after 2-3 days. Half-life of normeperidine = 15-20 h; not recommended in elderly or patients with impaired renal function; continuous IV infusion not recommended. The most appropriate candidates for meperidine use are patients with acute pain who are otherwise healthy and are allergic to other opioids, such as morphine and hydromorphone; or who require a faster onset of action but a short course of opioid treatment.
Methadone (Metadol)	PO, SL, R, IV, SC, IM, EA, IA	Long half-life can lead to delayed toxicity from accumulation at start of therapy and with each dose increment.
Oxycodone	PO (IR and CR), R	Used for moderate pain combined with a nonopioid (e.g., Percocet, Oxycocet). As single entity, can be used like oral morphine for severe pain. Controlled-release formulation available.
Oxymorphone (Numorphan)	IV, IM, SC, R	Used for moderate to severe pain. No oral preparation. Available in 5 mg rectal suppositories.
Propoxyphene (Darvon)	PO	Long half-life. Accumulation of toxic metabolite norpropoxyphene with repetitive dosing, not recommended for use in elderly.

CR, controlled-release (also called sustained-release or SR); EA, epidural analgesia; h, hour; IM, intramuscular; IR, immediate-release; IA, intrathecal analgesia; IV intravenous; mcg, microgram; mg, milligram; mL, milliliter; M6G, morphine-6-glucuronide; OTFC, oral transmucosal fentanyl citrate; PO, oral; q, every; PR, rectal; SC, subcutaneous; SL, sublingual; TD, transdermal; UK, unknown.

Adapted from McCaffery M, Pasero C: Pain: Clinical manual, pp. 179-180. Copyright © 1999, Mosby, Inc.

Table 5.11	Patient Considerations in the Treatment of Moderate to Severe Pain
Pain Intensity	• Background discomfort-mild pain may be managed with a nonopioid alone. • Mild-moderate pain may be managed with any opioid, but is usually managed with an opioid-nonopioid combination, such as codeine or oxycodone compounded with a nonopioid such as acetaminophen. • Moderate-severe pain is almost always managed with a strong opioid agonist which can be titrated upward as needed
Patient Age	Younger patients (with no major organ failure)- any opioid agonist Elderly patients (especially those with major organ failure) • Opioids with short half-life recommended (e.g. morphine, hydromorphone, oxycodone) • Opioids with long half-life avoided (e.g. methadone, levorphanol) • Opioids with active metabolites avoided (e.g. meperidine, propoxyphene)
Coexisting Disease	**Hepatic Failure:** • All opioid drugs are metabolized by the liver. • Liver disease- opioid clearance decreased; bioavailability & half-life increased • May increase adverse effects from higher than expected plasma concentrations • Metabolism of morphine & methadone- not significantly altered in liver disease **Renal disease:** • May accumulate the active metabolites of meperidine (normeperidine), propoxyphene (norpropoxyphene), and morphine (M6G) • Normeperidine eliminated by the kidneys: meperidine contraindicated in renal disease • Accumulation of morphine metabolite M6G- increased and prolonged effects • Hydromorphone recommended if morphine toxicity occurs in a patient with renal disease
Concurrent Drugs	Drug Interactions- see Tables 5.8 & 5.12 • Medication history to determine concurrent drug therapy; modify opioid choice if a potential interaction is identified
Prior Treatment Outcomes	History to include previous experience with the drug: • Unmanageable side effects with an opioid, explore whether the side effects were really unmanageable or simply unmanaged • True allergy to an opioid is extremely rare • If intolerable/unmanageable side effects, switch to another opioid

Patient Preferences and Convenience	• Respect patients' preferences (e.g. for the choice of opioid, route of administration, and scheduling of doses) whenever feasible
	• Preferences may be based on myths and misconceptions- ensure patient has factual information, including an accurate understanding of pain management.
	• Make opioid treatment regimen convenient- improved patient compliance with treatment plan
	  • Use CR opioid in place of short-acting opioid to reduce number and frequency of pills taken or consider fentanyl transdermal patch
	  • Schedule opioid doses concurrent with other medications, if possible

Cost	• Cost of medications and the amount of prescription insurance coverage can vary • Morphine, hydromorphone and methadone are less expensive than other opioids • Single opioids in sufficient doses may provide adequate pain control and minimize cost • Consider options to minimize cost to patients and family; poor compliance if drugs cannot be afforded • Patient assistance programs may be available to help patients who are unable to afford their analgesic medications.

Table 5.12 Drug Interactions with Opioid Analgesics

Drug Interactions Common to Drug Class:

Drug interactions which increase opioid effects:

- **hydroxyzine**- see below

Drug interactions which decrease opioid effects:

- **opioid antagonist agents, mixed agonist-antagonist opioids**- competitively decrease opioid analgesia

Drug interactions which increase opioid adverse effects:

- **anticholinergic drugs** (e.g. antihistamines, phenothiazines, tricyclic antidepressants, antiparkinsonian drugs)- may increase constipation, urinary retention with **opioids**
- **drugs which cause central nervous system depression & sedation** (e.g. antidepressants, phenothiazines, benzodiazepines, neuroleptics)- monitor opioid-induced sedation, respiratory depression carefully
- **antidiarrheal agents** (e.g. loperamide)- can increase constipation
- **hydroxyzine**- may increase analgesic effects, but also increase sedation, CNS depression and hypotension

Drug interactions in which opioids increase effects of other drug(s):

- **antihypertensive agents, diuretics, hypotension-causing agents** - increased hypotension

Drug interactions in which opioids decrease effects of other drug(s):

- **metoclopramide**- opioids may decrease promotility effect of metoclopramide

Agent-Specific Drug Interactions:

Drug interactions which increase opioid effects:

- **clomipramine**, **amitriptyline** (tricyclic antidepressants)- increase the bioavailability and half-life of **morphine**
- **amphetamines**- can increase analgesic effects of **meperidine, BUT with increased amphetamine toxicities** (potentially lethal)

Drug interactions which decrease opioid effects:

- **phenytoin, rifampin (& other CYP450 inducers)**- increase **methadone** metabolism, decrease plasma levels
- **rifampin**- can result in complete loss of **morphine** analgesic effects
- **urine acidifiers** (see Page 33)- decrease serum levels of **methadone**

Drug interactions which increase opioid adverse effects:

- **MAO inhibitors**- can precipitate excitation, hyperpyrexia, convulsions, and death with **meperidine**

Drug interactions in which opioids increase effects of other drug(s):

- **anticoagulants**- increased anticoagulant effects, bleeding with **meperidine**

In addition to the desired pharmacologic effect of analgesia, opioid receptors may also cause unwanted effects, or side effects. Different opioid agonists may affect one or more receptors, resulting in a different combination of side effects (Table 5.9). Opioids which have an agonist action at the Kappa receptor (e.g. butorphanol, pentazocine) may cause psychotomimetic effects and chronic sedation not normally associated with other opioid agonists.

Choice of Opioid Agonist Drug

- Only one opioid agonist by a single route of administration should be used whenever possible. Characteristics of several opioid agonists are outlined in Table 5.10
- At equianalgesic doses (i.e. doses which produce the equivalent amount of analgesic effect), there is very little difference between opioid agonists in their ability to relieve pain[29,31,32]. However, patients vary in their responsiveness (that is, their ability to achieve a favorable balance between pain relief and side effects) to the different drugs (see Tables 5.11, and 5.12). This is the reason to switch from one opioid agonist to another, and should only be considered if the dose of the first drug has been gradually increased (titrated) to determine whether it actually can provide adequate relief without intolerable side effects.
- Side effects vary between patients. Some individuals will have different side effects or more severe side effects from one opioid agonist than another. This cannot

be predicted unless the patient has had previous experience with the drug[29,33].

- The appearance of unmanageable and unacceptable side effects from an opioid agonist is one of the major reasons for switching to another opioid agonist. Before switching, determine whether the side effects are persistent and unmanageable (e.g., nausea cannot be managed with antiemetics) or simply unmanaged (e.g., no attempt was made to treat the nausea).
- If the dose of an opioid agonist relieves pain but causes unmanageable and unacceptable side effects, another opioid agonist should be used. Sequential trials may be necessary because considerable inter-individual variability exists in the occurrence, severity, and manageability of side effects.
- Opioid agonists which are metabolized to toxic active metabolites (e.g. norpropoxyphene from propoxyphene or normeperidine from meperidine) should not be used for treatment of chronic severe cancer pain.
- A true allergy to opioid agonist is very rare. Side effects are often reported in error as an allergy. If the patient has a true allergy to an opioid, such as morphine, another opioid, such as methadone or fentanyl, may be tolerated.
- For breakthrough pain[34,35], the opioid agonist selected should have a rapid onset and short duration of action, such as immediate-release morphine. Whenever possible, the opioid for breakthrough pain should be the same as the opioid used for continuous treatment.
- Other criteria for selection of one opioid over another may depend upon the individual patient. Some of these considerations are discussed in Table 5.8.

Characteristics of selected opioid agonists

Morphine

- Standard with which all other opioid drugs are compared[36]
- Most commonly used drug for cancer pain
    - Extensive research and clinical experience
    - Controlled-release formulations.
- Two main metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)[36,37]
    - M3G is the primary metabolite of morphine but it is not active at the opioid receptor
    - M6G is active at the opioid receptor
    - Some of the effects (both analgesia and side effects) are due to M6G
- Chronic oral morphine dosing- blood levels of M6G usually exceed those of morphine[29,30,38]
- There can be uncommon opioid toxicities (e.g. pronounced nausea and respiratory depression)
    - Often due to accumulation and high blood concentrations of M6G
    - More likely in patients with renal failure.
- Morphine has a short half life of 2 to 4 hours; the half-life of M6G is slightly longer[30,38]
- Does not persist in tissues; 24 hours after the last dose, tissue concentrations are low
- Only 40% of oral morphine dose remains after first pass effect (hepatic metabolism)
    - Recommended oral dose is higher than parenteral dose of morphine
- Dosing of morphine varies from one patient to the next
    - A simple dosing schedule (illustrated in Figure 5.3) may be useful for starting morphine in the opioid-naïve patient (i.e. a patient receiving chronic opioid dosing for the first time).

Codeine

- Limited use in the management of severe pain; codeine provides analgesia for mild pain only[39,40]
- Recommended maximum oral dose of 60 mg of codeine produces analgesia equal to 600 mg of aspirin
- Combination preparations of codeine and acetaminophen not appropriate for moderate to severe or escalating pain

Figure 5.3 Dose Titration Schedules for Morphine

A. Dose titration of immediate-release Morphine:
Doses given as mg PO q4h

5 ► 10 ► 15 ► 20 ► 25 ► 30 ► 40 ► 50 ► 60 ► 70 ► 80 ► 90 ► 100

Above 100 mg, dose increments of 20 to 30 mg, adjusting the dose every 16-24 hours.
A daily maximum of two dose increments is recommended (equivalent to 50-100% of previous dose)

B. Dose titration of parenteral Morphine:
Doses given as mg q4h (IV or SC)

2.5 ► 5 ► 7.5 ► 10 ► 12.5 ► 15 ► 20 ► 25 ► 30 ► 35 ► 40 ► 45 ► 50

Above 50 mg, dose increments of 10 to 15 mg.

C. Dose titration of sustained-release Morphine:
When stabilized on immediate-release Morphine, convert to sustained-release Morphine by dividing the total daily dosage by 2, and give as mg PO q12h. First dose may be given at the same time as the last dose of immediate-release Morphine. Adjust dose after 48 hours; if residual pain, adjust by increasing dose, not decreasing interval.

10 ► 15 ► 30 ► 45 ► 60 ► 90 ► 120 ► 150 ► 180 ► 200

Above 200 mg, dose increments of 30 to 60 mg, adjusting the dose every 48 hours.
If dose escalation results in icreased side effects during first few hours and/or inadequate analgesia in last hours of interval, consider dosing q8h with the same total daily dose.

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- Ceiling on the maximum safe daily doses of acetaminophen and aspirin limits dose increases for inadequate pain control
- Approximately 60% oral bioavailability; codeine undergoes less first pass metabolism than morphine
- Codeine is inactive until metabolized in the liver to morphine by CYP2D6 isoenzyme ; CYP2D6may be altered by interactions with some drugs (e.g. paroxetine, fluoxetine)
- Wide variations exist between individuals in terms of absorption and analgesic requirements of codeine.

Hydromorphone

- Hydromorphone is a reasonable choice for initial treatment of cancer pain
- Can be given by a variety of routes, including oral, rectal, SC, IM, IV, epidural, and intrathecal
- 30% to 40% bioavailable; oral to parenteral ratio of 2:1
  - Repeated dosing does not change this oral parenteral ratio- no analgesic metabolites that accumulate[41]
  - may be a better choice than morphine for patients with renal insufficiency, particularly the elderly
- More potent than morphine (i.e.equal analgesia with fewer milligrams of hydromorphone than morphine)
- Rapid onset (within 5 minutes after IV dose), short time to peak effect (10 to 20 minutes), and short duration (3 to 4 hours)[42].
- Short half-life (2 to 3 hours)
- Commercially available in a high-potency parenteral formulation (10 mg/mL)
  - Smaller injection or infusion volumes in patients who require opioid analgesics by parenteral administration
  - Important when opioids are delivered by the SC route[43]
  - Often used for SC intermittent bolus dosing and continuous SC infusions[44-47].
- A simple dosing schedule (Figure 5.4) may be useful for starting treatment in the opioid-naïve patient.

Fentanyl

- Transdermal patch and oral transmucosal fentanyl citrate formulations used for treatment of cancer pain
- Metabolized in the liver; no active metabolites[38]
- Short onset (within 1 to 5 minutes) and duration (less than 1 hour) of action, when given as a single IV bolus
- Terminal half-life of approximately 3 to 4 hours (at steady state); half-life with transdermal fentanyl is increased to 13 to 24 hours[48,49].
- Transdermal fentanyl is not generally recommended as the initial opioid
  - May be started once the patient is stabilized on another opioid.
- Useful when when there are GI absorption problems, when patients have difficulty with compliance, or if opioid rotation is considered for excessive side effects from a previous agent[50,51]
- Incidence of constipation[52,53] and sedation[54] is lower with transdermal fentanyl than with oral morphine
- Conversion from oral morphine (or equivalent) is calculated from the total daily dose equivalent, then titrated for the individual (Table 5.13)
- Transdermal patches are available in multiples of 25, 50, 75 or 100 mcg/hr, and are effective for 72 hours per patch
  - Patch cannot be cut for partial doses.
  - Takes 10-16 hours to reach peak effect, so the short-action opioid should be continued for at least 12 hours when switching to the patch.

Oxycodone

- May be used to treat cancer pain of moderate to severe intensity.
- Available as combination product compounded with a nonopioid, such as acetaminophen (use restricted to mild-moderate pain), and as oral single entity drug product in both immediate-release and controlled-release formulations.
- Metabolized in the liver to its active

Figure 5.4 Dose Titration Schedules for Hydromorphone

A. Dose titration of immediate-release Hydromorphone:
Doses given as mg PO q4h

1 ► 2 ► 3 ► 4 ► 5 ► 6 ► 8 ► 10 ► 12 ► 14 ► 16 ► 18 ► 20

Above 20 mg, dose increments of 4 to 6 mg, adjusting the dose every 16-24 hours.
A daily maximum of two dose increments is recommended (equivalent to 50-100% of previous dose)

B. Dose titration of parenteral Hydromorphone:
Doses given as mg q4h (IV or SC)

0.5 ► 1 ► 1.5 ► 2 ► 2.5 ► 3 ► 4 ► 5 ► 6 ► 7 ► 8 ► 9 ► 10

Above 10 mg, dose increments of 2 to 3 mg.

C. Dose titration of sustained-release Hydromorphone:
When stabilized on immediate-release Hydromorphone, convert to sustained-release Hydromorphone by dividing the total daily dosage by 2, and give as mg PO q12h. First dose may be given at the same time as the last dose of immediate-release Hydromorphone. Adjust dose after 48 hours; if residual pain, adjust by increasing dose, not decreasing interval.

3 ► 6 ► 9 ► 12 ► 18 ► 24 ► 30 ► 36 ► 42 ► 48

Above 48 mg, dose increments of 6 to 12 mg, adjusting the dose every 48 hours.
If dose escalation results in icreased side effects during first few hours and/or inadequate analgesia in last hours of interval, consider dosing q8h with the same total daily dose.

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Table 5.13 Dosing of Transdermal Fentanyl

- To convert from an opioid to transdermal fentanyl (Duragesic), first calculate the 24 hour oral morphine equivalent dose, then locate the equivalent fentanyl dose on the chart below
- Continue the original opioid for 12-24 hours after the first transdermal patch is applied, to allow the patch to create a reservoir under the skin
- Apply on a dry, hairless area of the skin (that has not been irradiated). To remove hair, do not shave but clip off the hairs. Apply a new patch every 72 hours, on a different skin site
- Transdermal fentanyl should NOT be given as initial treatment to an opioid naive patient

Morphine to Transdermal Fentanyl Conversion

Oral Morphine Dose per 24 hrs.	Parenteral Morphine Dose per 24 hrs.	Fentanyl Patch Dose (mcg/hr)
45-134 mg	15-44 mg	25
135-224 mg	45-74 mg	50
225-314 mg	75-104 mg	75
315-404 mg	105-134 mg	100
405-494 mg	135-164 mg	125
495-584 mg	165-194 mg	150

- For ease of conversion, consider 50-100 mg of oral morphine in 24 hours equal to 25mcg/hr transdermal fentanyl
- This conversion table is very conservative- the initial dose may be increased in the second 72 hour period, based on the number of breakthrough doses required in the initial 72 hours. It takes 6 days to reach steady state after each doage adjustment.
- Breakthrough opioid medication- use 5-10 mg morphine/ 1-2 mg hydromorphone PO q1 hr PRN for each 25 mcg/hr fentanyl

metabolite, oxymorphone

- Oral bioavailability of 50% to 80%, with a short half-life (3 to 4 hours)
- Less toxic than equianalgesic doses of codeine.

Oxymorphone

- May be used for moderate to severe pain
- Quick onset (5 to 10 minutes after IV dose); peak time is 15 minutes; duration of 3 to 6 hours; half-life of 2 to 3 hours.
- Well absorbed by IM, SC, and IV routes
- Commercially available as a rectal suppository but no oral formulation; onset of action is 15 to 30 minutes after rectal dose, with a peak time of 120 minutes

Methadone

- Synthetic opioid, chemically unrelated to the opiate (morphine-like) molecule
- Known for its use in narcotic withdrawal and maintenance programs for drug addicts, giving this drug a negative connotation in the public perception
- In Canada, physicians require a special authorization from Health Canada to be allowed to prescribe methadone
- Relatively inexpensive, compared with other commercial opioid products
- For treatment of cancer pain, some clinicians limit the use of methadone to patients for whom cost and access to prescription opioids are real obstacles and to those who exhibit a true allergy to morphine[55]
- Current research suggests that methadone may be active at NMDA (N-Methyl-D-Aspartate) receptors as well as opioid receptors, suggesting an additional role for this drug in treatment of cancer pain with neuropathic characteristics[56].
- Oral methadone is well absorbed and has an oral bioavailability of 85% (significantly higher than morphine)[57]
- Lower parenteral/oral potency ratio of 1:2 compared with 1:6 for single-dose morphine
- Redistributes extensively into muscle and fat
- Onset of analgesia similar to morphine; peak plasma concentrations peak 2 hours after oral administration; duration of analgesia 4 to 8 hours.
- Extensively metabolized in the liver; long and variable half-life of methadone (12 to 190 hours); wide inter-individual variability in the clearance of methadone, but much lower than other opioid drugs
  - Long time to reach steady state after dosing is initiated or changed
  - Maximum analgesic effect of the

dosing regimen cannot be determined until steady state
- Days or weeks of drug accumulation may occur after a period of rapid dose titration- delayed onset of adverse effects
- Methadone considered a poor choice for patients who are difficult to monitor or are predisposed to opioid side effects (e.g. elderly, noncompliant patients, patients with major organ failure)
- Incomplete cross-tolerance in opioid-tolerant patients
- Switching to methadone may be an option for treatment of intolerable and unmanageable side effects or for improving analgesia in cases of escalating dose requirements with other opioid agonists

Figure 5.5 Dosing of Oral Methadone for Cancer Pain

- Prescribers are required to have a methadone licence (from Health Canada) to prescribe this agent
- It is suggested to consult with a prescriber with methadone expertise when considering the use of methadone
- Equianalgesic conversion ratios from other opioids to methadone may vary based upon the dose of the opioid at time of conversion
- There are several methods for converting from another opioid to methadone. Two methods are described below:

Step 1.
Determine target Methadone dose

Oral morphine 24 hours dose equivalent

≤ 500mg ► Methadone dose at Methadone 1: Morphine 10 ratio

> 500mg ► Methadone dose at Methadone 1: Morphine20 ratio

Step 2.
Titrate Methadone dose over 3 days

Day 1:
- 2/3 of the original opioid plus 1/3 of the calculated total dose of the methadone (in 3 divided doses q8h)
- Use original opioid for breakthrough pain

Day 2:
- 1/3 of the original opioid plus 2/3 of the calculated total dose of the methadone (in 3 divided doses q8h)
- Use original opioid for breakthrough pain

Day 3:
- Discontinue the original opioid and give the full calculated methadone target dose(in 3 divided doses q8h), as tolerated
- Convert to methadone for breakthrough pain[1] when pain is stable

Oral Methadone given in divided doses TID (may be BID or QID)

Alternate Step 2

- Decrease calculated total dose of the methadone by 1/3 (for incomplete cross-tolerance), give adjusted methadone dose (in 3 divided doses q8h) on days 1 & 2; discontinue regular doses of original opioid but use original opioid for breakthrough pain during titration
- Titrate methadone dose every 48 hours, as needed
- Convert to methadone for breakthrough pain[1] when pain is stable

1. Consider 10% of total daily methadone dose given q2-3h for breakthrough pain

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- Traditional equianalgesic estimates (e.g., 20 mg of methadone orally being equal to 30 mg of morphine orally) based on single doses of opioids for opioid-naive patients- inappropriate starting doses of oral methadone for opioid-tolerant patients
- When switching these patients to methadone, it is almost like starting treatment in an opioid-naive patient
- Target dose for starting methadone calculated at a 1:10 ratio to the total daily oral morphine equivalent, or less if the morphine equivalent is high (1:20 ratio if > 500 mg per day)- see Figure 5.5.
- Titration will take three days during conversion from another opioid, with gradual methadone dose increases as the other opioid is weaned off[28], as illustrated in Figure 5.5.
- Some clinicians use other methods for drug conversion,- the rule is to 'start low and go slow'
- Can be administered by the rectal route, although commercial rectal preparations are not available
    - Custom-made suppositories are sometimes prepared for use in by local pharmacy
- In one study[28], improved pain relief and substantial cost savings demonstrated when cancer patients switched from hydromorphone subcutaneously by continuous infusion to methadone suppositories.

Meperidine

- Meperidine should **not** be used for long-term treatment of cancer pain
- Continues to be commonly used as an opioid analgesic for the management of pain despite evidence that it is not appropriate as a first-line opioid analgesic for the management of any type of pain[1]
- Appeal of meperidine may be rapid onset of action and peak effect, and short duration of action
    - Other opioids, such as hydromorphone, have comparable features and no toxic metabolites.
    - Poor oral absorption of meperidine requires large doses when given PO
- Major drawback to meperidine is the active metabolite, normeperidine (which produces neurotoxicity)
    - CNS stimulant- can produce irritability, tremors, muscle twitching, jerking, agitation, and seizures
    - Half-life of 15 to 20 hours, compared with the short half-life of meperidine[30]
    - If meperidine used for chronic pain management, the metabolite will accumulate over time
    - Normeperidine eliminated by renal excretion, so meperidine should not be used in patients with decreased renal function or the elderly[30]
    - Normeperidine may partially antagonize the effects of meperidine and lead to dose escalation for analgesia
    - If meperidine is decreased abruptly, neurologic toxicities may be worsened and an anticonvulsant should be considered.
- Meperidine should only be considered for patients with acute pain who are otherwise healthy and are allergic to other opioids, such as morphine and hydromorphone, or have demonstrated a more favorable outcome with meperidine than other opioid drugs
    - Frequent high doses should be avoided
    - Course of treatment should be restricted to no more than a few days with the dosage limited to 600 mg within a 24-hour period
    - Evaluate patients frequently (i.e. every 8 to 12 hours) for signs of CNS irritability, specifically restlessness, shakiness, tremors, twitching, and jerking.

5.5.1 Opioid Dose Titration

Titration of the opioid dose usually is required at the initiation of therapy to find the individual dose level, and frequently during the course of treatment, as cancer pain progresses. The absolute opioid dose is not important as long as the balance between pain relief and side effects is acceptable. There is no clear association between plasma concentrations of the opioid and pain relief[60], so subjective assessment must be the guide for titration. The goal of titration is to use the smallest dose that provides satisfactory pain relief with the fewest side effects.

The first sign that an increase in opioid dose is needed is most commonly a decrease in the duration of analgesia for a given opioid dose. For example, a patient taking a controlled-release opioid may report breakthrough pain occurring invariably toward the end of the continuous analgesic dosing interval, such as in the 11th hour of a 12-hour dosing schedule. Patients also may report the need for an increased number of rescue doses. As a rule of thumb, two or more rescue doses during a 12-hour period (four to six daily) should alert the clinician that the opioid dose may need to be increased.

When an increase in the opioid dose is necessary, the first step is to calculate the total daily dose, by adding the around-the-clock (ATC) doses and the average number of breakthrough pain (BTP), or rescue doses used daily[3]. (This may exclude any of the BTP doses used for incident pain, such as a dose given prior to physiotherapy or some other predictable painful event). The ATC dose is increased to the new total daily dose (divided into appropriate dosing intervals), and a new BTP dose may be recalculated based on the increased ATC dose. If there was residual pain, despite the use of BTP doses, the new ATC dosage may also be proportionately increased above the recalculated dose, as indicated in Table 5.14. If there is only mild residual pain remaining after the previous opioid dose, an increase of 10% may be sufficient; for moderate residual pain, a 10-25% increase, and for severe residual pain, a 50-100% increase may be indicated. The time at which the dose should be increased is typically determined by considering the onset or peak effect of the opioid. For example, titration of oral opioid doses may occur as often as every 1 to 2 hours (for severe, uncontrolled pain; usually no more often than 2-3 times per day), whereas titration of oral controlled-release opioids may occur every 24 to 48 hours. As a general rule opioid titration should 'start low and go slow'.

Patients should be involved in the decision to increase the opioid dose. It is important to understand the pattern of pain described by the patient, and their concerns about compliance with the opioid regimen. For example, patients commonly take more rescue doses during the times when they are active than when they are resting. Patients with cancer pain who work or are particularly active frequently take more than two rescue doses during a 12-hour period. Many patients would prefer to administer additional BTP doses during these periods of activity rather than risk increased sedation that can accompany an increase in the ATC opioid dose. Some patients may prefer less than complete pain relief rather than risk nausea or sedation with an increased dose.

Tolerance

Tolerance refers to a process characterized by decreasing effects of a drug at a constant dose of the drug or the need for a higher dose of drug to maintain an analgesic effect[29]. Continued exposure to the drug is the primary cause of tolerance. In terms of tolerance to opioid drugs, it is a physiologic response that should be expected when an individual takes an opioid drug for several days or longer. Tolerance to analgesia may be evident after a few days of treatment. The first indication of tolerance is most commonly a decrease in the duration of analgesia for a given opioid dose followed by a decrease

Table 5.14 Dose Titration of Opioids

For Mild Pain:

- Calculate the total 24 hour dose (include all regular and PRN doses), divide by 6, consider increasing dose by 10%, give this dose q4h ATC[1]
- BTP[2] dose (10% of new 24h dose, or 1/3 to 1/2 of regular q4h dose(or 1/5 of q12h for sustained-release opioid dose); give q1h PRN)
  - BTP dose can be given at the same as the regular dose, if needed
- Reassess at least every 48-72 hours

For Moderate Pain:

- Calculate the total 24 hour dose (include all regular and PRN doses), increase by 10-25%, divide by 6, give this dose q4h ATC[1]
- BTP[2] dose (10% of new 24h dose, or 1/3 to 1/2 of regular q4h dose; give q1h PRN)
  - BTP dose can be given at the same as the regular dose, if needed
- Reassess at least every 24 hours

For Severe Pain:

- Calculate the total 24 hour dose (include all regular and PRN doses), increase by 25-50%, divide by 6, give this dose q4h ATC[1]
- BTP[2] dose (10% of new 24h dose, or 1/3 to 1/2 of regular q4h dose; give q1h PRN)
  - BTP dose can be given at the same as the regular dose, if needed
- Reassess at least every 12 hours
- Reassessment may be needed more often than every 24 hours; this may be done by the patient or health caregiver

Continue antiemetics and laxatives

1. ATC = around-the-clock
2. BTP = breakthrough pain

in analgesic effect. Tolerance can be managed easily, usually by increasing the opioid dose. Careful attention to pain assessment is necessary during the first few days of opioid treatment, to adjust for tolerance development. Once the dose is titrated to an acceptable level, it should not need to be frequently changed if the pain is stable.

Tolerance should not be confused with addiction, and it is not a predictor of abuse[30]. It occurs regardless of why the opioid is used. Persons taking opioids for either pain relief or those abusing opioids will likely develop tolerance to some drug effects. If the opioid analgesic effect is reduced due to progression of the cancer or a psychologic cause, this is not tolerance. Unfortunately, disease progression is often the reason that opioid doses require continuing titration in cancer patients[29,38,61]. Clinicians should not delay initiating opioid analgesic treatment or withhold opioid dose increases from patients for fear of producing tolerance or reaching a dose beyond which no further analgesia can be obtained.

It is important to reinforce information about tolerance and ceiling effect to patients and families because they are often reluctant to begin opioid analgesic treatment. They may also be concerned that the effectiveness of opioid analgesics will diminish over time and that the patient will be subjected to severe pain in later stages of disease if the opioid is started too early[29].

Tolerance also develops to some of the opioid side effects, such as nausea, sedation or respiratory depression[29,38]. Usually these side effects are worse in the first days and decline within a few days after initiation or dose increase of an opioid analgesic. Other side effects, such as constipation, do not develop any tolerance over time[62].

TABLE 5.15 Preventing and Managing Opioid-Induced Side Effects

Side Effect	Prevention	Management

Constipation	Begin all patients on ATC opioids with a laxative bowel regimen
	• Sennosides (eg. Senokot) 8.6mg 1-2 tablets PO QHS *OR*
	• Sennosides (as above) plus Docusate Sodium (eg. Colace) 100mg 1-2 caplets PO BID *OR*
	• Docusate-Senna combination (eg. Senokot-S) 1-2 tablets PO QHS
		If no BM in any 48 h period, add one to two of the following:
		• Sennosides 2 tabs QHS to 4 tabs TID
		• Bisacodyl (Dulcolax) 5 mg PO QHS to 15 mg PO TID
		• Milk of Magnesia 30 to 60 mL QD or BID
		• Lactulose (Chronulac: 10g/15 ml) 15 to 60 mL QD or BID
		If no BM by 72 h (and not neutropenic), perform rectal examination to rule out impaction.
		If **not impacted**, try one of the following:
		• Bisacodyl (Dulcolax) suppository 10 mg
		• Magnesium citrate 8 oz PO
		• Mineral oil 30 to 60 ml PO
		• Milk of magnesia 25 mL + cascara 5 mL suspension
		• Fleet enema
		If **impacted**:
		• Administer rescue analgesic or tranquilizer before disimpaction.
		• Manually disimpact if stool is soft
		• If not, soften with glycerin suppository or oil retention enema, then disimpact manually
		  • Note: Disimpact with caution if neutropenic or thrombocytopenic
		• Follow up with enema (tap water, soapsuds) until clear
		• Increase daily bowel regimen
		• In patients with refractory constipation consider use of
		  • A prokinetic agent (e.g. metoclopramide or domperidone)
		  • Oral administration of naloxone to produce "bowel withdrawal" without concurrent systemic withdrawal. Starting at 0.8 mg bid and doubling the dose q 2 to 3 days until a favorable response, increased pain, or signs of withdrawal

Nausea, vomiting	• Titrate opioid doses slowly and steadily.
	• Add or increase nonopioid or adjuvant for additional pain relief so that the opioid dose can be reduced.
	• If analgesia is satisfactory, reduce opioid dose by 25%.
		• Investigate for other causes of nausea (e.g. constipation, other medications)
		• Try metoclopramide 5 to 10 mg q4h SC or PO or domperidone 10 to 40 mg PO QID
		• If nausea persists, add dexamethasone 10 mg BID
		• If nausea persists, add other antiemetics:
		  • Haloperidol 0.5 to 2 mg daily PO or SC- may go to 5 mg
		  • Prochlorperazine 5 to 10 mg PO or IM q4-6h PRN
		• See ***Guidelines for the Management of Nausea and Vomiting in Cancer Patients***

Pruritus	• Consider rotation or dose reduction of opioid	• Diphenhydramine 12.5-25 mg IV or 25-50 mg PO may be given to alleviate symptoms, but is sedating • Naloxone (0.8 mg/1000 mL) IV infusion titrated to effect is generally used only after other steps have failed.

TABLE 5.15 Preventing and Managing Opioid-Induced Side Effects (continued)

Side Effect	Prevention	Management
Sedation	• Consider rotation or dose reduction of opioid • Consider giving a lower opioid dose more frequently to decrease peak concentration • Assess for other sedating medications • Eliminate nonessential CNS depressant medications • Assess for other causes for sedation (eg. exhaustion, metabolic disorders)	• Consider steroids- Dexamethasone 4-8 mg PO/SC QD • Consider psychostimulant- Methylphenidate (Ritalin) 2.5-5mg PO QD-BID • Educate patients that they may be drowsy for a few days when starting an opioid or after increasing the dose
Respiratory depression	• Monitor sedation level and respiratory status during the first 24 h in opioid-naive patients treated for moderate to severe pain • Consider rotation or dose reduction of opioid	• If patient is minimally responsive or unresponsive to stimulation, stop opioid administration and consider administering naloxone (Note: administer with caution in patients on chronic opioid therapy)
Neurological Symptoms (eg.myoclonus, hyperalgesia/ allodynia, mental confusion, hallucinations, delirium, paranoia, nightmares)	• Consider rotation or dose reduction of opioid • Consider reversible causes (eg. metabolic disorders, liver or renal dysfunction) or irreversible causes (eg. organic brain disease); treat underlying process if appropriate • Eliminate nonessential CNS-acting medications, e.g., steroids	Specific symptoms: • Myoclonus- Consider Clonazepam 0.5-1 mg PO QD-TID or or Valproic Acid 5 mg/Kg PO TID • Nightmares- Consider Clonazepam 0.5-1 mg PO QD-TID, Haloperidol 2.5-5 mg HS, or Methotrimeprazine 5 mg PO HS • Hallucinations- Consider Haloperidol 1-5 mg q4h PRN • Delirium or agitation- Consider Haloperidol 2.5-5 mg PO/SC q6-12h PRN or Midazolam 2-5 mg SC stat then 30 mg/24 hr SC infusion or 5 mg SC q1h • Avoid using naloxone, even if delirium is thought to be due to the opioid

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5.5.2 Opioid Maintenance

Once the pain is stable and adequately controlled, a maintenance opioid regimen may be considered. Although short-acting opioids may continue to be used ATC, patients and families will find it difficult to comply with frequent daily dosing, especially doses required through the night. A controlled-release (CR) opioid product is often desirable for long term treatment[9,27]. Some opioids with CR formulations include morphine, hydromorphone, oxycodone and transdermal fentanyl.

If possible, one of the above agents should be used for initial analgesic treatment and titration, to facilitate conversion to its CR product. Conversion is a simple process, by calculating total 24 hour dose (include all regular and PRN doses, dividing by two, and giving this dose as the CR oral opioid product every 12 hours). BTP doses should also be ordered, calculated as 10% of the total 24 hour dose (or about 1/5 of the q12h sustained-release opioid dose), and give q1h PRN. Continue the antiemetics as needed and the regular bowel regimen (i.e. laxatives) during maintenance treatment.

For some patients, it may be useful to change the opioid agonist to transdermal fentanyl for maintenance of stable cancer pain (see Table 5.13 for conversion chart). Transdermal fentanyl may be chosen for patients who cannot tolerate oral opioids due to GI absorption problems, for patients who have difficulty complying with a regimen of oral tablets, or for patients experiencing excessive side effects from a previous agent.

5.5.3 Opioid side effects or toxicities

Opioid **side effects** are common undesirable symptoms resulting from opioids. These side effects may be temporary or preventable. They usually respond to therapeutic management when they occur[62].

In opioid-naive patients, common opioid side effects include constipation, nausea and vomiting, sedation, respiratory depression, pruritus, and mental confusion and clouding. As the patient becomes opioid tolerant, these side effects tend to subside, except for constipation. Individual patients vary in the development of opioid-induced side effects.

Prevention of opioid side effects is as important as treatment[63] (see Table 5.15). Most side effects are dose dependent. One approach is to ensure the optimal use of nonopioids and non-sedating adjuvant analgesics, so that the lowest effective opioid dose can be given. For some patients, simply decreasing the opioid dose is sufficient to eliminate or make a side effect tolerable. Decreases in opioid doses can be accomplished by percentages. If the side effect is mild, 25% may be appropriate; for more effect, 50% to 100% may be appropriate.

Opioid **toxicities** are exaggerated responses to the known side effects of opioids. Opioid toxicity usually refers to neurological symptoms, but may also include urinary retention or unmanagable nausea. These adverse effects are more difficult to prevent or manage. Opioid toxicities usually require opioid dose reduction (see Section 5.5.5) or rotation (see Section 5.5.4). A sequential series of steps to manage opioid toxicity is illustrated in Figure 5.6, which also includes optimization of hydration to reduce accumulation of opioids and opioid metabolites as possible contributors to toxicity.

GI dysfunction

- Constipation is the most common opioid side effect; no tolerance develops[40,62,64-67]
  - Opioids delay gastric emptying, slow

bowel motility, decrease peristalsis, and reduce secretions from the colonic mucosa

  - Result is slow moving, hard stool that is difficult to pass
  - Can result in ileus, fecal impaction, and obstruction
- Constipation best managed by prevention, regular assessment, and aggressive management if symptoms are detected[40]
- All patients on opioid analgesics should be directed to take laxatives regularly, continue as long as opioids taken
  - Combination of stool softener (e.g. docusate) and mild peristaltic stimulant (e.g. sennosides) is recommended; stool softener alone may not be adequate[67]
  - Use oral laxatives if possible, even if opioid given by different route (e.g. transdermal fentanyl)[68]
  - Bulk laxatives (e.g. psyllium (Metamucil®)), natural roughage, and large amounts of fluid may be unpalatable and ineffective; if fluid intake is inadequate, bulk laxatives can cause fecal impaction
- Aggravating factors include advanced age, immobility, abdominal disease, and concurrent medications
- If uncontrolled, constipation may become severe and present as ileus and pseudo bowel obstuction
  - Continuous IV metoclopramide[69] and orally administered naloxone[70-71] have been reported for management of severe constipation.

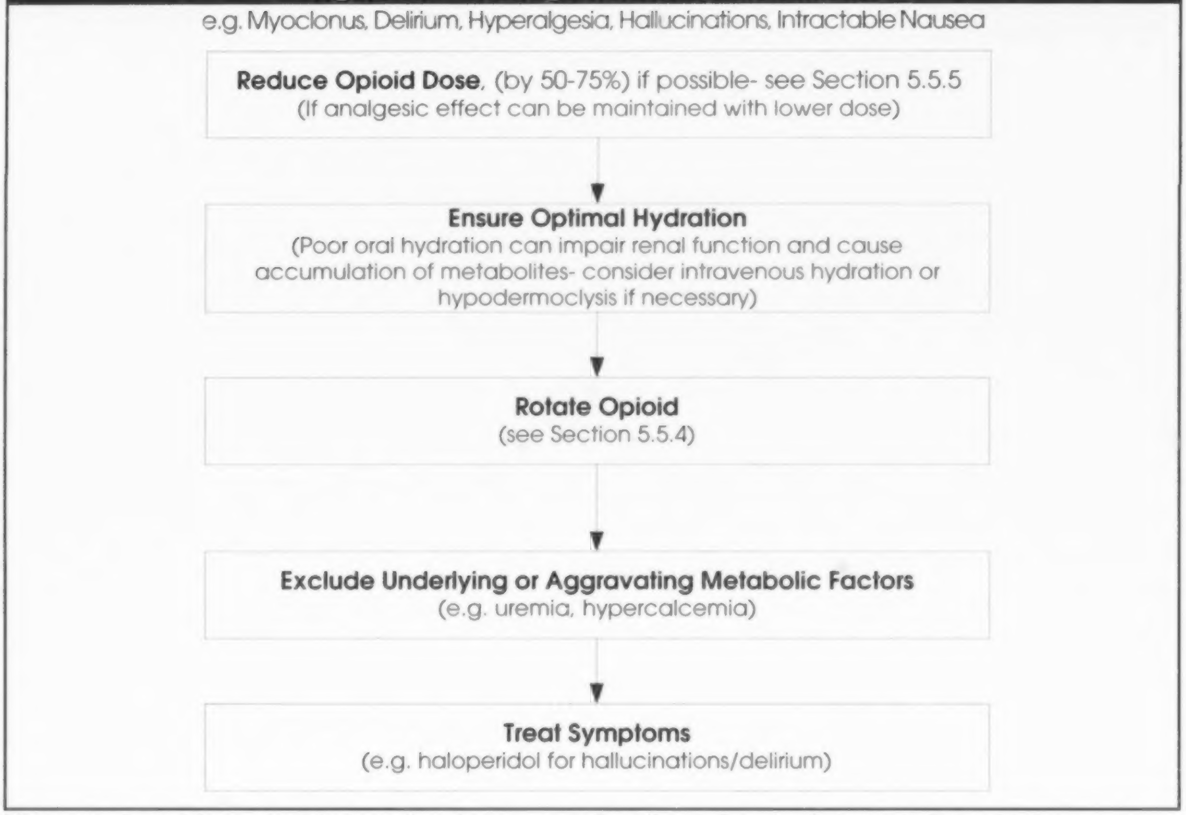
Nausea and Vomiting

- Nausea is the most common side effect with initial opioid doses; usually subsides within weeks of opioid therapy[72-74]
  - Initiating or increasing opioid therapy may cause nausea by stimulating the chemoreceptor trigger zone in the brain, slowing GI mobility, and sensitizing the vestibular system (needed for balance and equilibrium)[75-78]
- Prophylactic treatment of nausea not recommended- most effective antiemetics produce sedation and other undesirable effects[40,79]
- Slow and steady opioid titration helps to reduce nausea
- If nausea is a consistent problem, antiemetic drugs may be given prophylactically; prokinetic agents (metoclopramide or domperidone) are recommended for first line treatment of opioid-induced nausea[80,81]; ensure patient has access to proper antiemetic drug in the home[69]
- Changes in diet and activity, or the use of relaxation techniques may be helpful[9]
- For more information, see ***CCNS Guidelines for the Management of Nausea and Vomiting in Cancer Patients***

Pruritus

- Pruritus (itching) is the most common side effect when opioids are delivered by the intraspinal route[63]
  - Sometimes generalized all over the body but usually localized to the face, neck, or upper thorax
  - Due to cephalad migration of the opioid in CSF and subsequent interaction in the medulla
  - Does not appear to be related to histamine release from mast cells
- Most effective treatment for pruritus- decrease opioid dose
  - If opioid given by continuous epidural infusion, reduce opioid dose by addition or dose increase of nonopioid or local anesthetic in the epidural opioid solution
- Antihistamines may relieve symptoms of pruritus, probably by sedative effects

Figure 5.6 Management of Opioid Toxicity



e.g. Myoclonus, Delirium, Hyperalgesia, Hallucinations, Intractable Nausea

Reduce Opioid Dose, (by 50-75%) if possible- see Section 5.5.5
(If analgesic effect can be maintained with lower dose)

Ensure Optimal Hydration
(Poor oral hydration can impair renal function and cause accumulation of metabolites- consider intravenous hydration or hypodermoclysis if necessary)

Rotate Opioid
(see Section 5.5.4)

Exclude Underlying or Aggravating Metabolic Factors
(e.g. uremia, hypercalcemia)

Treat Symptoms
(e.g. haloperidol for hallucinations/delirium)

May be duplicated for use in clinical practice. As appears in: Broadfield L, Banerjee S, Jewers H, Pollett AJ, Simpson J., Guidelines for the Management of Cancer-Related Pain in Adults. © *Cancer Care Nova Scotia*, 2005

Sedation

- Sedation common with initial opioid dose and when dose is increased; usually subsides within a few days (tolerance development)[50]
    - If significantly sedated, discourage patients from driving or operating mechanical equipment, until sedation subsides
    - Sedation may be confused with exhaustion, the need to "catch up" on sleep when poorly controlled pain is finally controlled[9]
    - Patient education should include an understanding that sedation is anticipated, but usually temporary (i.e. no more than 2 to 3 days for most patients)
- If untreated, excessive sedation progresses to clinically significant opioid-induced respiratory depression in opioid-naive patients
- Decrease opioid dose to treat sedation, if possible[79]
    - May give lower opioid dose more frequently to decrease peak concentration- may be effective to reduce sedation
- Take a medication history for other drugs which may be sedating (e.g. muscle relaxants, anxiolytics)- consider dose-reduction or elimination of other drugs
- Screen for other underlying conditions that cause sedation, such as metabolic disturbances
- Adding a psychostimulant is a treatment option for sedation
    - Methylphenidate (Ritalin®) or dextroamphetamine- start at 2.5 to 5 mg in the morning and repeat midday; doses can be titrated upward to 40 mg daily
- If unacceptable sedation persists, rotate to another opioid

- Consider intraspinal opioids and/or local anesthetics or neurolysis when other approaches fail or are not possible[9]

Respiratory depression

- Clinically significant respiratory depression is feared as an opioid-induced side effect.
    - Respiratory depression described as clinically significant when there is a decrease in rate and depth of respirations from baseline (not just by a specific number of respirations per minute)[79]
    - Tolerance to respiratory depression develops over a period of days to weeks (or less for some patients)
- All opioid naive patients are at risk for clinically significant respiratory depression with their first dose of an opioid
    - Increased risk- infants less than 6 months old, elderly opioid-naive patients, comorbid conditions such as chronic pulmonary disease or major organ failure[79]
- Prevention by careful opioid titration and close monitoring of sedation and respiratory status in first 24 hours (or longer)[40,79]
- Progressive (hours to days) somnolence and respiratory depression and pinpoint pupils may indicate subacute overdose, which is more common than acute respiratory depression[3]
    - Risk of subacute overdose is higher during titration of opioids with long half-lives (e.g. methadone, levorphanol)
    - Withhold one or two opioid doses until the symptoms have resolved, then reduce the ongoing opioid dose by 25%
- Reversing clinically significant respiratory depression may be achieved by careful titration of naloxone[82,83]
    - More than one dose of naloxone may be necessary, due to short duration (1 hour) of effect
    - If naloxone dose is too high or if it is given too fast- can precipitate severe pain and increase sympathetic activity (leading to hypertension, tachycardia, ventricular dysrhythmias, pulmonary edema, and cardiac arrest)

Biliary spasm

- Any opioids may increase smooth muscle tone in the biliary tract, especially constricture of the sphincter of Oddi[76,83]
- Can result in decrease of biliary and pancreatic secretions, rise in bile duct pressure- can last up to 12 hours
- Experience epigastric distress and occasionally biliary spasm

Mental status changes

- Confusion, disorientation, and cognitive impairment feared by patients and families[85-87]
- Mild cognitive impairment and occasional hallucinations may occur when opioid therapy is initiated and with significant dose increases- transient, resolve within a few days[9,40,88]
- Opioids may contribute to delirium in the terminally ill (manifestations include hallucinations, disorientation, clouding consciousness, fear, and paranoia)
- Management of opioid-induced cognitive and other neurotoxic side effects begins with dose reduction and hydration, and may progress to opioid rotation or a change in opioid route of administration[89]; follow steps to resolve opioid toxicity (Figure 5.6)

Myoclonus

- Mild myoclonus (uncontrolled muscle movements, trembling) is common, may resolve as tolerance develops[9,40]
- Myoclonic jerks- only in patients receiving high doses of opioids for types of pain that are the least responsive to opioids (e.g. incident pain from bony metastasis, neuropathic pain)[90]
    - Most common with meperidine, from normeperidine accumulation[91,92]
- Clonazepam 0.25 to 0.5 mg orally two or three times daily, helps to control jerking but is sedating

5.5.4 Opioid Rotation

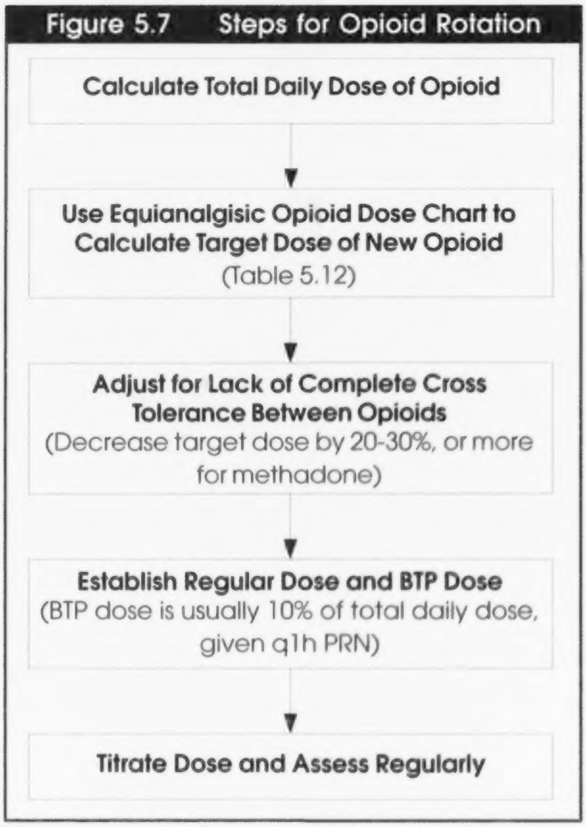
When toxicities or side effects to opioid analgesics limit the titration, one method to manage the pain without excessive toxicity is to switch to another opioid. This is referred to as opioid rotation[93-99].

There is little difference between most opioid agonists in their ability to relieve pain. Analgesia is related to dose rather than opioid agent. Unrelieved pain is usually best managed by continued dose titration, possibly with the addition of a nonopioid analgesic or adjuvant drugs. Reasons to rotate opioid include:

- Intolerable or unmanageable side effects
- Difficulty adhering to an analgesic regimen (e.g. too many pills, too frequent doses)
- Reduction of cost for long-term opioid treatment

The variability between individuals can result in differences of efficacy between different opioids. When switching an opioid-tolerant patient to an alternative opioid drug, cross-tolerance will not likely be complete. This means that a patient who has developed tolerance to one opioid analgesic may not be equally tolerant to another. Therefore when switching to a new opioid, opioid-tolerant patients should be started on one half (50%) to two thirds (66%) of the equianalgesic dose of the new opioid if pain is controlled. This is especially the case when switching to methadone, where there is very little cross-tolerance. If the patient has been taking a high dose of opioid, it is best not to abruptly discontinue the present opioid and convert to the new in one step. This could cause a significant overdose that precipitates undesirable side effects or an underdose that precipitates severe pain. Instead, it is best to make the transition with 50% of the current opioid dose combined with 50% of the projected dose for the new opioid for several days. From this starting point, gradual increases in the new opioid drug and decreases in the old can be made until the switch is complete. The higher the dose of the current opioid, the more important it is to make the transition using 50/50 dosing.

Figure 5.7 Steps for Opioid Rotation



Calculate Total Daily Dose of Opioid

Use Equianalgisic Opioid Dose Chart to Calculate Target Dose of New Opioid
(Table 5.12)

Adjust for Lack of Complete Cross Tolerance Between Opioids
(Decrease target dose by 20-30%, or more for methadone)

Establish Regular Dose and BTP Dose
(BTP dose is usually 10% of total daily dose, given q1h PRN)

Titrate Dose and Assess Regularly

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Opioid dose conversions- Using the equianalgesic chart (Table 5.16)

The term equianalgesia means approximately the same pain relief when patients are given doses of various opioid analgesics. The equianalgesic chart (Table 5.16) provides a list of analgesics at doses, both oral and parenteral, that are approximately equal to each other in the ability to provide pain relief. Many of the dose comparisons are based on single doses compared with morphine 10 mg IM. There is some controversy over the usefulness of an equianalgesic chart, since there is substantial variability between patients in the individual response to different opioids, and because the analgesic effects change

Table 5.16 Equianalgesic Opioid Dose Chart

Opioid	Parenteral (IM/SC/IV) (over ~ 4 h)	Oral (PO) (over ~ 4 h)	Onset (min)	Peak (min)	Duration[1] (h)	Half-life (h)
Opioid Agonists						
Morphine	10 mg	20(-30) mg Chronic use 60 mg Acute use	30-60 (PO) 30-60 (CR)[2] 30-60 (PR) 5-10 (IV) 10-20 (SC,IM)	60-90 (PO) 90-180 (CR)[2] 60-90 (PR) 15-30 (IV) 30-60 (SC,IM)	3-6 (PO) 8-12 (CR)[2] 4-5 (PR) 3-4 (IV)[1,3] 3-4 (SC,IM)	2-4
Codeine	120 mg	200 mg NR	30-60 (PO) 10-20 (SC,IM)	60-90 (PO) UK (SC) 30-60 (IM)	3-4 (PO) 3-4 (SC,IM)	2-4
Hydromorphone	2 mg (1.5 mg[4])	4-6 mg (7.5 mg)	15-30 (PO) 30-60 (CR)[5] 15-30 (PR) 5 (IV) 10-20 (SC,IM)	30-90 (PO) 290 (CR) 30-90 (PR) 10-20 (IV) 30-90 (SC,IM)	3-4 (PO) 12 CR) 3-4 (PR) 3-4 (IV)[1,3] 3-4 (SC,IM)	2-3
Fentanyl	100 mcg/h parenterally and transdermally = 4 mg/h morphine parenterally; 1 mcg/h transdermally = morphine 2 mg/24 h orally	—	5 (OT) 1-5 (IV) 7-15 (IM) 12-16 h (TD)	15 (OT) 3-5 (IV) 10-20 (IM) 24 h (TD)	2-5 (OT) 0.5-4 (IV)[1,3] 0.5-4 (IM) 48-72 (TD)	3-4[6] 13-24(TD)
Levorphanol	2 mg	4 mg	10-60 (PO)		4-8 (PO)	11-16
Oxycodone	10 mg (7 mg with chronic use)	20 mg (15 mg with chronic use)	30-60 (PO) 30-60 (CR)[7] 30-60 (PR)	60-90 (PO) 90-180 (CR)[7] 30-60 (PR)	3-4 (PO) 8-12 (CR)[7] 3-6 (PR)	2-3 4.5 (CR)
Oxymorphone	1-1.5 mg	(5-10 mg PR)	15-30 (PR) 5-10 (IV) 10-20 (SC,IM)	120 (PR) 15-30 (IV) UK (SC) 30-90 (IM)	3-6 (PR) 3-4 (IV)[1,3] 3-6 (SC,IM)	2-3
Methadone	10 mg[7]	20 mg[9]	30-60 (PO) UK (SL) 10 (IV) 10-20 (SC,IM)	60-120 (PO) 10 (SL) UK (IV) 60-120 (SC,IM)	4-8 (PO) UK (SL) 4-8 (IV)[1,3] 4-8 (SC,IM)	12-190
Meperidine Not recommended for chronic use	75 mg	200-300 mg	30-60 (PO) 5-10 (IV) 10-20 (SC,IM)	60-90 (PO) 10-15 (IV) 15-30 (SC,IM)	2-4 (PO) 2-4 (IV)[1,3] 2-4 (SC,IM)	2-3
Agonist-antagonists						
Buprenorphine[10]	0.4 mg	—	5 (SL) 5 (IV) 10-20 (IM)	30-60 (SL) 10-20 (IV) 30-60 (IM)	UK (SL) 3-4 (IV)[1,3] 3-6 (IM)	2-3
Butorphanol[10]	2 mg	—	5-15 (NS)[11] 5 (IV) 10-20 (IM)	60-90 (NS) 10-20 (IV) 30-60 (IM)	3-4 (NS) 3-4 (IV)[1,3] 3-4 (IM)	3-4
Dezocine	10 mg	—	5 (IV) 10-20 (IM)	UK (IV) 30-60 (IM)	3-4 (IV)[1,3] 3-4 (IM)	2-3
Nalbuphine[9]	10 mg	—	5 (IV) <15 (SC) <15 (IM)	10-20 (IV) UK (SC) 30-60 (IM)	3-4 (IV)[1,3] 3-4 (SC) 3-4 (IM)	5
Pentazocine[9]	60 mg	180 mg	15-30 (PO) 5 (IV) 15-20 (SC,IM)	60-180 (PO) 15 (IV) 60 (SC,IM)	3-4 (PO) 3-4 (IV)[1,3] 3-4 (SC,IM)	2-3

Footnotes: See next page

somewhat with long term regular dosing and tolerance development[100].

A patient's pain intensity and the equianalgesic chart are practical tools to use to determine an appropriate opioid starting dose for an opioid-naive patient. All the opioid doses listed in the *equianalgesic chart are appropriate* starting doses given about every 4 hours for adults with severe pain.

5.5.5 Opioid dose reduction

Most opioid side effects and toxicities are dose-related (except for constipation). Occasionally, dose titration may overshoot the optimal opioid dose, and result in toxicity with no additional analgesia. If the type of pain responds poorly to opioids (e.g. neuropathic pain), increasing opioid doses will not improve pain control. In these circumstances, the opioid dose may be reduced, as a strategy for side effect/ toxicity management[89].

Dose reduction should be considered in context of the individual patient problem. If the pain may respond to a nonopioid or adjuvant, these medications should be explored and optimized. It is not effective to mix multiple opioids together with lower doses of each- this will not reduce side effects. If the pain has decreased (e.g. after neurosurgery or in the weeks following radiotherapy to a bony metastasis), opioid dosage may be titrated downward. In addition, non-pharmacologic methods for pain relief may be considered as one means by which opioid dose reduction could be managed. The key to success is careful and ongoing assessment, and timely reaction to the assessment findings.

Footnotes (Table 5.16)

ATC, around-the-clock; CR, oral controlled-release; h, hour; IM, intramuscular; IV intravenous; mcg, microgram; mg, milligram; min, minute; NR, not recommended;
NS, nasal spray; OT oral transmucosal; PO, oral; PR, rectal; SC, subcutaneous; SL, sublingual; TD, transdermal; UK, unknown.

[1] Duration of analgesia is dose dependent; the higher the dose, usually the longer the duration.

[2] e.g., MS Contin.

[3] IV boluses may be used to produce analgesia that lasts approximately as long as IM or SC doses. However, of all routes of administration, IV produces the highest peak concentration of the drug, and the peak concentration is associated with the highest level of toxicity (e.g., sedation). To decrease the peak effect and lower the level of toxicity, IV boluses may be administered more slowly (e.g., 10 mg of morphine over a 15-minute period) or smaller doses may be administered more often (e.g., 5 mg of morphine every 1-1.5 hours).

[4] The recommendation that 1.5 mg of parenteral hydromorphone is approximately equal to 10 mg of parenteral morphine is based on single dose studies. With repeated dosing of hydromorphone (e.g., PCA), it is more likely that 2-3 mg of parenteral hydromorphone is equal to 10 mg of parenteral morphine.

[5] e.g., Hydromorph Contin.

[6] At steady state, slow release of fentanyl from storage in tissues can result in a prolonged half-life of up to 12 hr.

[7] e.g., OxyContin.

[8] In opioid-tolerant patients converted from continuous IV hydromorphone to continuous IV methadone, start with 10%-25% of the equianalgesic dose.

[9] In opioid-tolerant patients converted to methadone, see Figure 5.5 for conversion.

[10] Used in combination with opioid agonists, may reverse analgesia and precipitate withdrawal in opioid-dependent patients.

[11] In opioid-naive patients who are taking occasional mu agonists, such as codeine or oxycodone, the addition of butorphanol nasal spray may provide additive analgesia. However, in opioid-tolerant patients, such as those receiving ATC morphine, the addition of butorphanol nasal spray should be avoided because it may reverse analgesia and precipitate withdrawal.

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TABLE 5.17 Routes of Opioid Administration

ROUTE	COMMENTS
Oral	• inexpensive, simple, noninvasive; should be considered before all other routes • preferred in cancer pain management • opioids are subject to extensive hepatic metabolism; slow onset but just as effective as other routes if doses are high enough and given ATC
Oral transmucosal	• oral transmucosal fentanyl citrate (OTFC) has been shown to be effective and convenient in managing breakthrough pain in patients with cancer pain • bypasses significant hepatic metabolism
Buccal	• generally unavailable and impractical
Sublingual	• buprenorphine, fentanyl, and methadone absorbed well • morphine may be used by the sublingual route, but research is limited
Rectal	• morphine, oxymorphone, and hydromorphone are commercially available • alternative for patients unable or unwilling to take analgesics orally • considerable variation in dose required to produce effect and time to reach effect; starting dose usually is same dose as oral dose • may be compounded by pharmacy for rectal administration or given in an aqueous solution, unmodified tablet, or crushed and placed in gelatin capsule; controlled-release formulations should not be crushed or dissolved
Transdermal	• fentanyl citrate drug delivery system incorporated within an adhesive patch can provide analgesia for 48-72 h by continuous drug release into the skin • slow onset, gradual decline after patch is removed • alternative for patients unable or unwilling to take analgesics orally or have failed other opioids and could benefit from a trial • not suitable for acute pain or severe escalating pain
Nebulized	• not recommended as a route for analgesia; very little absorption of analgesic
Subcutaneous • Single or repetitive bolus • CI with or without PCA	• morphine & hydromorphone most common subcutaneous opioids • alternative when patient is unable to take opioid orally or parenteral route is indicated but venous access is limited • easy access, but technique and care require skill and expertise • infusion pumps for continuous infusion (CI); newer pumps allow PCA capability; CI adds expense but useful when frequent SC injections become difficult for patient
Intravenous • Single or repetitive bolus • CI with or without PCA	• indicated when rapid titration required; opioids with short half-life recommended; duration dose dependent • when steady state reached by CI, opioid agonists differ little in terms of duration • for long-term CI, permanent venous access is recommended; indicated for cancer pain when patient has dose-limiting side effects from other systemic routes; not usually given to ambulatory patients
Epidural • Single or repetitive bolus • CI with or without PCA	• rarely indicated for cancer pain management (e.g., may be alternative for patients with dose-limiting side effects from systemic opioid analgesics) • infusion pumps add expense, but allow for continuous infusion and PCA capability • duration is dose dependent; when steady state is reached by continuous infusion, opioid agonists differ little in terms of duration • for patients with cancer pain and long life expectancy, may be administered by external catheter and pump or by implanted infusion pump. Local anesthetics may be added to opioids by this route

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5.5.6 Change route of opioids

See Table 5.17

Opioids should be administered by the least invasive and safest route of administration[39]. Only one route of administration at a time should be used. The oral route should always be considered before other routes because it is relatively safe, convenient, and inexpensive. If rapid onset of analgesia is desired, the IV route is used. Over time, however, more than one route of administration may become necessary. For example, in patients with progressive cancer pain more than half required more than one route of administration to maintain pain control during the last four weeks of life[101]. This occurred usually when patients were unable to swallow. Other routes of administration are available and are indicated in certain situations. For patients unable or unwilling to take medications by the oral route, noninvasive alternatives are available.

Oral

- Preferred route for administering opioids to patients with chronic pain; can be taken by most patients
- Flexible dosing, produces steady analgesic blood levels
- Adequate route for a wide range of pain intensities, from mild to severe pain
- Most opioid agonists are available in oral form
- Two major disadvantages of the oral route:
  - Slow onset of action and delayed peak time (90 to 120 minutes after ingestion and longer in the case of controlled-release (CR) tablets)- inappropriate for severe, escalating pain
  - Intervals between doses of immediate-release (IR) preparations remain short (usually q4 hours)- six doses a day, which may interfere with sleeping; compliance can be difficult
- Some patients cannot take medications orally due to GI obstruction or difficulty swallowing[9,27]
  - Some opioids are available in liquid form (e.g. morphine), and others may be crushed and mixed with pureed foods or liquid (for administration through nasogastric or other feeding tubes). Generally, sustained-release products should not be crushed, although there is at least one morphine preparation (M-Eselon capsules) which may be opened and sprinkled over food or poured into feeding tubes. Check with the pharmacy for specific products available as liquid or crushable tablets/capsules.
- Absorption can be altered by several factors, including presence of food, gastric emptying time, and GI motility. CR preparations appear to be less affected by the presence of food than IR preparations.
- CR opioid preparations make oral route more convenient- doses given only once or twice a day (see Opioid Maintenance, section 5.5.2)

Oral transmucosal

- Absorption from the oral transmucosa optimal for drugs that are lipid soluble, such as fentanyl, buprenorphine, and methadone[illegible]
- Three areas within the mouth for oral transmucosal drug delivery: sublingual (SL), buccal, & gingival areas; SL is best for drug permeability

Sublingual

- Sublingual route involves placing the drug under the tongue for absorption
- Drug is absorbed directly into systemic circulation, avoiding first pass effect[illegible]
- Few opioids administered by the sublingual route
- Drug absorption not affected by concentration, but by contact time (must be in contact with the oral mucosa at least 5 minutes)
- Side effects are minor (bitter taste, burning sensation, light-headedness)
- No commercially available preparations, high doses cannot be given[9]

Oral Transmucosal Fentanyl Citrate (OTFC)

- Fentanyl has formulated as a lozenge (on a stick, like a lollypop)- available in other countries
  - To administer OTFC, patients instructed to suck on the lozenge and, holding onto the stick, move it around the inside of the mouth and gums and above and below the tongue so that it dissolves in the saliva
  - Compared with oral fentanyl administration, OTFC yields higher and more rapid plasma concentrations and greater bioavailability[illegible]
  - Onset of analgesia more consistent and rapid than by the oral route of administration, side effects will dissipate quickly when discontinued
- OTFC useful for breakthrough pain (BTP), especially when patients receiving transdermal fentanyl as regular opioid[illegible]

Rectal

- Rectal route- inexpensive alternative to the oral route
- When patients unable to take oral medications, parenteral routes may be avoided[illegible]
- All opioid analgesics may be administered rectally; if not commercially available, may be compounded for rectal administration[illegible]
- Effective dose of rectal opioids approximately equal to oral dosing
- Indications: persistent or temporary nausea and vomiting, GI tract obstruction, or mental status changes, other routes are unavailable
- Contraindications: neutropenia or thrombopenia (potential rectal bleeding from insertion of the suppository)[illegible]
- Major disadvantage- many individuals find it objectionable, reluctant to take rectal drugs
- Rectal administration of CR opioid products- good absorption and slow, steady release; more prolonged time to peak by the rectal vs. oral route[illegible]
  - CR formulations must not be crushed or dissolved.

Transdermal

- Fentanyl is the only opioid available by the transdermal route[112,113]
- Fentanyl highly lipophilic- ideal for absorption into the skin
  - Skin under the drug reservoir absorbs fentanyl, depots of the drug concentrate in the upper skin layers, fat, and skeletal muscles
  - Gradual release into systemic circulation
  - Transdermal system provides continuous release at a nearly constant rate for 72 hours
- Fentanyl transdermal system incorporated within an adhesive patch (see Table 5.9 for dosing information)- multiple patches may be applied to achieve a desired dose, but may be limited by the available skin area
- Indications: moderate to severe cancer pain with stable pain pattern that requires continuous opioid treatment & cannot be managed by oral opioids[50,51]
- Convenience of the transdermal route may help patients adhere to the treatment plan
- Cachetic patients absorb fentanyl by the transdermal route as well as patients with more body fat
- Major drawbacks: 12 to 16 hours for onset of analgesic effect with first dose; titration to an effective dose may require days; difficult to adjust dose in the management of side effects.
  - IR preparations of oral opioids, such as morphine, are administered PRN during the transition

Intramuscular (IM)

- IM route of administration is **not** recommended for pain management[27]
- Numerous disadvantages (e.g. painful administration, unreliable absorption, slow onset of analgesic peak effect, rapid drop in action) and essentially no advantages

Subcutaneous (SC)

- SC route for patients who experience dose-limiting side effects with oral opioids or require parenteral opioids because of bowel obstruction but have limited venous access[114,115]
- No need for normal GI function
- Absorption and distribution vary depending on the placement of the needle and the amount of adipose tissue (fat tissue); however, cachexia is not a contraindication to SC analgesia
- Continuous SC infusion (CSCI) of opioids in place of intermittent SC injections- popular alternative route for patients with chronic cancer pain who are unable to take oral medications and who do not have central venous access[44]
- Most common opioid analgesics administered by CSCI are hydromorphone and morphine; methadone not recommended due to local tissue irritation by this route
- Patients prefer CSCI over IV infusion- easier mobility, better pain control
- CSCI disadvantages: painful route, time consuming, and often disliked by patients
- Technique of administration is relatively simple, but more difficult than the oral route
- Sterile technique must be used, and the patient and caregivers must become familiar and skilled in the use of needles, syringes, an infusion pump, and other equipment
- SC injection site must be changed at least weekly; volume that can be infused or bolused must be limited to prevent irritation, pain, necrosis, and sloughing at the site
- High-concentration opioid formulations are used for CSCI infusion
- Most patients can absorb 2 or 3 mL/h, and some as much as 5 mL/h
- Rescue doses provided as SC boluses
- Successful home administration of CSCI depends on the ability of the family and community health care system to manage the technology in the home
- Cost and insurance coverage must be considered
- When establishing a plan for parenteral opioid analgesic infusion in the home, determine who will assume primary responsibility for the infusion technology, patient and family education regarding the infusion and pain and side effect assessment, and monitoring and follow-up

Intravenous (IV)

- IV route most efficient for an immediate analgesic effect (e.g. acute, severe escalating pain)
- IV route may be used temporarily for patients with cancer pain who require rapid titration or as an alternative for patients who are unable to take oral opioid analgesics[9]
    - Most commonly used for short courses of therapy in a hospitalized setting; patients closely monitored
- Methods of IV administration include bolus, continuous infusion, and PCA
- Duration of analgesia by bolus administration is dose dependent; the higher the dose, usually the longer the duration
- IV doses produce the highest peak concentration of the drug, associated with the highest level of toxicity (e.g., sedation, nausea)
- In terminally ill patients, bowel obstruction and dose-limiting side effects with other systemic opioids are reasons for long-term IV infusion through central catheters
- Drawbacks: depends on ability to maintain patent venous access; sterile technique is required to prevent systemic infection; more expensive; requires more expertise than the oral route

Intraspinal (epidural and intrathecal)

- "Intraspinal" refers to the spaces surrounding the spinal cord into which medications can be administered
- Refers to epidural and intrathecal routes of administration
- Patient selection guidelines and considerations in Table 5.18; should not be considered for routine use, but limit to selected patients[116,117]
- Intraspinal needle and catheter insertion

performed by an anaesthesiologist

- Delivery of intraspinal analgesics[118]:
  - Insert a needle into the subarachnoid space (for intrathecal analgesia) or the epidural space and injecting the analgesic
  - Thread a catheter through the needle and tape in place temporarily for bolus dosing or continuous administration; usually removed after two to four days
  - Risk of CNS infection; technically difficult
- For severe intractable chronic pain- long-term epidural catheter can be inserted, tunnelled subcutaneously for intermittent bolusing or continuous infusion by an external ambulatory pump
- Can be used for weeks to months to deliver analgesics
- Three methods for administering intraspinal analgesia:
  - Bolus (administered by the clinician)
  - Continuous infusion (administered by a pump)
  - Patient-controlled epidural analgesia (administered by the patient usually using a pump).
- Drugs administered intraspinally are extremely potent (i.e., very small doses are effective) because distribution of the drug brings it close to the action site (opioid receptors in the dorsal horn of the spinal cord)
- Dose of an opioid by the intraspinal routes is much smaller than required by the parenteral route to produce equal analgesia
- Two main types of drugs administered intraspinally to treat pain: opioids and local anesthetics
  - Morphine[119] and fentanyl[120] most common opioids administered by intraspinal route
  - Local anesthetics often combined with epidural opioids for the treatment of pain[118,121]
  - Epidural local anesthetics often administered, but long-term intrathecal use is controversial due to potential for neurotoxicity[121]
  - Low ("subanesthetic") doses of local anesthetics work synergistically with intraspinal opioids to provide better analgesia at lower doses than would be possible with the opioid alone[119]
  - Lower incidence of adverse effects of both opioids and local anesthetics
  - Low concentrations of the lipid soluble

TABLE 5.18 Use of Intraspinal Analgesia in Cancer Pain

Patient Selection

- Absence of contraindications to epidural needle/catheter placement (e.g., coagulopathies, abnormal clotting studies, sepsis, history of multiple abscesses).
- For patients with chronic pain, systemic opioid therapy produces unmanageable and intolerable side effects.
- Patient has a pain syndrome that may be responsive to a specific intraspinal therapy such as local anesthetics, clonidine, or steroids (e.g., neuropathic pain unresponsive to oral adjuvant analgesics).[1]
- In the patient with cancer pain who will receive long-term intraspinal opioid therapy, a reduction in pain in response to a trial dose of an intraspinally administered opioid has been experienced.[1]

Other Considerations

- Appropriate equipment and supplies are available for therapy.
- Staff (or family) are trained to assess and manage epidural analgesia.
- Clinical support systems available ATC if needed.

Medical Conditions for Which Intraspinal Analgesia Is Commonly Prescribed

- Intractable cancer pain
- Intractable neuropathic pain
- Myocardial ischemia unresponsive to conventional treatment

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amide-type local anesthetics used most often- bupivacaine 0.0625-0.125% (Marcaine) and ropivacaine 0.2% (Naropin)[122,123]

- Adverse reactions: allergy is uncommon; vascular uptake can result in CNS systemic toxicity (ringing in ears, metallic taste, slow speech, irritability, twitching, seizures), or cardiotoxicity (circumoral tingling and numbness, bradycardia, cardiac dysrhythmias, acidosis, cardiovascular collapse)[124]
- Complications: postdural puncture headache, intraspinal catheter migration, and neurologic complications from neural tissue trauma, neurotoxic agents, infection, and hematoma.

5.6 Adjuvant Analgesic Agents

An adjuvant analgesic is a drug that has a primary indication other than pain but is analgesic in some painful conditions. Although these drugs are usually added to an opioid, in certain conditions they may be used alone[125]. Adjuvant analgesics have been used mostly in the treatment of chronic pain of neuropathic origin, but this role has expanded to cover other pain disorders[126-129]. Some common adjuvant analgesics and nonopioids are illustrated in Figure 5.8.

Some adjuvant analgesics are effective for many different pain syndromes. These multipurpose adjuvant analgesics include antidepressants, corticosteroids, and alpha2-adrenergic agonists (e.g., clonidine).

5.6.1 Antidepressant Drugs

- Indication: neuropathic pain which has not responded to opioids[126-129]
- Two major groups: tricyclics and the "newer" antidepressants. See Table 5.19
  - Tricyclic antidepressants are analgesic in a variety of chronic pain syndromes[130]
  - "Newer" antidepressants- less definitive study results[131,132]
  - Clinical interest in the SSRIs, because of their relatively good side effect profile[133]
- Analgesic effect of these drugs does not depend on antidepressant activity[133-139]
- Analgesic dose lower than antidepressant dose; onset of analgesia occurs much sooner, usually within 1 week
- Mechanism of action- block reuptake of neurotransmitters (e.g. serotonin, norepinephrine) in the central nervous system; increase activity in endogenous pain-modulating pathways[140-142]
- Serious adverse effects are uncommon; less serious side effects are frequent
  - Orthostatic hypotension, sedation and mental clouding, anticholinergic side effects (e.g. dry mouth, blurred vision, constipation, decrease in salivation), sexual dysfunction, cardiotoxicity (rare)
- Drug selection: consider amitriptyline 10-25 mg PO daily, unless concerned about

toxicity; other options to consider- desipramine 10-25 mg PO daily or an SSRI agent
  - Titrate dose upwards every 3-5 days until pain relief or adverse events

5.6.2 Corticosteroids

- Indicated for medical management of epidural spinal cord compression, raised intracranial pressure, and superior vena cava syndrome
- May also be effective in reflex sympathetic dystrophy (a type of neuropathic pain) and diverse types of cancer pain[145,146] (e.g. bone pain, neuropathic pain from infiltration or compression of neural structures, headache caused by increased intracranial pressure, painful lymphedema, arthralgia, pain caused by organ capsule distention, and pain caused by obstruction of hollow viscus (e.g., bowel or ureter))
- Exact mechanism of action unknown[147-151]
  - May reduce peritumoral edema and relieve compression of pain-sensitive structures[152]
  - May reduce tissue concentrations of some inflammatory mediators (e.g. prostaglandins and leukotrienes), and thus reduce nociceptor activation
  - May lessen aberrant electrical activity in damaged nerves[153]
- Drug selection[126-129]: relative risks and benefits of the various corticosteroids are unknown, but dexamethasone is usually selected; prednisone and methylprednisolone may also be used
  - Clinical equivalencies: methylprednisolone 8 mg = prednisone 10 mg = dexamethasone 2 mg.
- Dose selection: usually administered either in a high-dose regimen or a low-dose regimen
  - High-dose- dexamethasone 96 mg/day in divided doses for rapidly worsening malignant plexopathy(see Table 5.26), superior vena cava syndrome, or epidural spinal cord compression (oncologic emergencies); taper dose over weeks, concurrent with other analgesic approaches, such as radiotherapy[154]
  - Low-dose- dexamethasone 1-2 mg once or twice daily over a long term for advanced cancer with pain despite optimal dosing of opioid drugs[126]; prednisone 7.5 mg to 10 mg for bone pain in prostate cancer
- Adverse effects with short-term and long-term administration of corticosteroids:
  - Short-term- neuropsychologic effects, hyperglycermia, fluid retention, and gastrointestinal disturbances ranging from dyspepsia to bowel perforation (may need to avoid concurrent administration with NSAIDs)
  - Long-term- cushingoid appearance (moon face, buffalo hump); skin diseases and changes in subcutaneous and connective tissues; weight gain; hypertension; severe osteoporosis; myopathy; increased risk of infection; hyperglycemia; gastrointestinal toxicity; and late neuropsychologic effects
  - Steroid withdrawal after chronic therapy- can produce a syndrome of

TABLE 5.19
Antidepressant Adjuvant Analgesics

	Tricyclic Antidepressants
Tertiary amines	Amitriptyline (Elavil®) Clomipramine (Anafranil®) Doxepin (Sinequan®) Imipramine (Tofranil®)
Secondary amines	Desipramine (Norpramin®) Nortriptyline (Aventyl®)
	"Newer' Antidepressants
Phenethylamine	Venlafaxine (Effexor®)
Triazolopyridine	Trazodone (Desyrel®) Nefazodone (Serzone®)
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine (Prozac®) Paroxetine (Paxil®) Sertraline (Zoloft®)
Tetracyclic	Maprotiline (Ludiomil®)
Aminoketone	Bupropion (Wellbutrin®)

Adapted from McCaffery M, Pasero C: Pain: Clinical manual, p. 306. Copyright © 1999, Mosby, Inc.

muscle and joint pain (known as steroid "pseudorheumatism"), malaise, headache, and mood disturbance, or a pain flare; escalate steroid dose and then taper dose more gradually

5.6.3 Other Drugs With Non-specific Analgesic Effects

Dextroamphetamine and Methylphenidate:

- Psychostimulant drugs have some analgesic effects, as well as their usefulness to manage sedation and cognitive impairment caused by opioids and other sedating drugs[155-157]

Figure 5.8 Adjuvant Drugs for Cancer Pain Management

In addition to optimal opioid therapy

Neuropathic Pain ►

Tricyclic Antidepressant
- Amitriptyline 10 to 25 mg qHS, Nortriptyline 10 to 25 mg qHS or Desipramine 25 mg qHS

AND/OR

Antiepileptic drugs
- Gabapentin 100-300 mg qHS, Carbamazepine 100-200 mg BID, Valproate 250 mg daily to TID

AND/OR

Corticosteroid
- Dexamethasone 4 mg PO qAM (avoid concurrent administration with NSAID)

AND/OR

Ketamine 5-10 mg PO BID (refer to pain specialist for initiation and titration)

AND/OR

Non-Pharmacologic Approaches:
- Consider radiotherapy, surgical decompression, TENS, nerve blocks

Malignant Bone Pain ►

Acetaminophen 325-650 mg q4h PO

AND/OR

Non-Steroidal Anti-Inflammatory Agent PO (NSAID)
- Common Examples: Ibuprofen 200-800 mg TID, Naproxen 250-500 mg BID, Diclofenac 25-50 mg TID or 75 mg SR daily, Celecoxib 100-200 mg QD-BID

AND/OR

Corticosteroid
- Dexamethasone 4 mg PO qAM (avoid concurrent administration with NSAID)

AND/OR

Bisphosphonate
- Pamidronate 60-90 mg IV every 3-4 weeks

AND/OR

Non-Pharmacologic Approaches:
- Consider radiotherapy, physiotherapy, prophylactic subluxation, or fixation (if fracture present)

Incident Pain (Pain on mobilization) ►

Sufentanil 5-50 mcg SL/buccal, **Fentanyl** 200 mcg SL/buccal

Ketamine 0.125-1 mg/Kg SC

Non-Pharmacologic Approaches:
- Sling, splint, crutches, cane, walker, physiotherapy/occupational therapy

Pain from Compression or distention of tissues ►

Corticosteroid (as above)

AND/OR

Non-Pharmacologic Approaches:
- Consider radiotherapy, surgical decompression

See: Table 5.22 for more details on drug dosing

May be duplicated for use in clinical practice. As appears in: Broadfield L, Banerjee S, Jewers H, Pollett AJ, Simpson J., Guidelines for the Management of Cancer-Related Pain in Adults. © *Cancer Care Nova Scotia,* 2005

- Dosage: 2.5 to 5 mg in the morning (may add a second dose at midday, if necessary)
  - Increase dose daily up to 40 mg/day in divided doses, or higher
- Adverse effects include insomnia, anorexia, tremulousness, anxiety, agitation, and uncomfortable cognitive changes
- Indications: limited to use in decreasing opioid-induced side effects, such as sedation
  - High potential for abuse, and rapid analgesic tolerance development

Caffeine:

- Caffeine at doses of 65 to 130 mg orally provides modest analgesia[158,159]
- Analgesia is enhanced when a nonopioid is combined with caffeine; minimum dose is 65 mg
- Available in medications and food items, particularly coffee and tea

TABLE 5.20 Adjuvant Analgesics For Continuous Neuropathic Pain (Continuous Dysesthesias)

Class	Examples
Usually Tried First	
Antidepressants	Amitriptyline, desipramine
Systemic local anesthetics	Mexiletine, tocainide, flecainide
Gabapentin	
For Refractory Cases	
Alpha$_2$-adrenergic agonists	Clonidine
Anticonvulsants	Carbamazepine, phenytoin, valproate, clonazepam
Topical agents	Capsaicin, local anesthetics
Neuroleptics	Prochlorperazine, haloperidol
NMDA receptor antagonists	Dextromethorphan, ketamine
Calcitonin	
Baclofen	

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5.7 Management of Neuropathic Pain

Management includes the use of appropriate and effective drug therapy, along with other non-pharmacologic interventions. Nerve blocks and neurosurgery may be indicated, and, where appropriate, other physical interventions. Psychosocial and spiritual support may be needed as well, to help with total pain and suffering associated with chronic pain, especially if drugs and physical interventions are not completely effective.

5.7.1 Chronic Continuous Neuropathic Pain

Continuous dysesthesias are often described as continuous burning, electrical, or other abnormal sensations. Use of adjuvant analgesics are individualized, but common options are outlined in Table 5.20

Antidepressants:

- First-line treatment option

Oral and Parenteral (Systemic) Local Anesthetics

- Used in three major ways:
  1. For localized anesthesia by injection into tissues or near major nerves (nerve blocks), or intraspinal administration
  2. For localized analgesia by absorption of a topical application (e.g., lidocaine patch or eutectic mixture of local anesthetics (EMLA)).
  3. For generalized analgesia by systemic administration (oral or parenteral)
- Mechanism of action: local anesthetics block sodium channels and cause a nondepolarizing conduction block of the action potential[1,160]
  - Systemic local anesthetic drugs suppress aberrant electrical activity or hypersensitivity in neural structures (i.e. neuromas, dorsal root ganglion cells) involved in causing the pain
- Indications: second-line drugs for neuropathic pain- continuous dysesthesias nonresponsive to other adjuvant analgesics[162] (i.e. antidepressant, gabapentin), patient who cannot tolerate other adjuvants, long-term management of opioid-refractory neuropathic pain

- Drug selection: mexiletine first choice due to least likelihood of serious toxicity[126,127,129]
  - Start at 150 mg once or twice per day, increase every few days to a maximum dose of 300 mg three times per day
  - If mexiletine is not effective, consider trial with tocainide or flecainide

Alpha$_2$-Adrenergic Agonists

- Indications: limited to neuropathic pain not relieved with opioids and not responsive to other adjuvant analgesics (e.g. antidepressants, oral local anesthetics, anticonvulsants)[162-165]
- Mechanism of action is not clear, but likely involves alpha$_2$ noradrenergic recepors (in the spinal[166,167] or brain stem[168]) involvement with modulation of nociceptive processing
  - May interfere with sympathetically maintained pain mechanisms (subtype of neuropathic pain)
- Treatment begins with low dose oral clonidine (0.1 mg per day), with a gradual dose escalation until significant side effects or unacceptable hypotension[126,127,129,165]
  - Intraspinal clonidine may be considered on referral to a pain specialist (e.g. anesthetist)
- Most common adverse effects- sedation, hypotension (usually orthostatic), and dry mouth[165]
  - May be more severe in frail palliative patients

5.7.2 Chronic Lancinating ("'Shooting'") Neuropathic Pain

Lancinating neuropathic pain is described as sharp, shooting, stabbing, knifelike, and often sudden in onset. Anticonvulsants and baclofen, a gamma-aminobutyric acid (GABA) agonist, are first-line analgesics for this type of pain. Baclofen is only useful in the treatment of lancinating or paroxysmal neuropathic pain. Anticonvulsants may be effective analgesics for other types of neuropathic pain, but are considered only in refratory cases of this type of neuropathic pain. Other adjuvants are also useful for lancinating types of pain (Table 5.21).

Anticonvulsant Drugs

- Indications:
  - Gabapentin may be considered for all types of neuropathic pain[169-173]
  - Other anticonvulsant drugs considered first-line treatment for lancinating and other episodic paroxysmal neuropathic pains[126-129,174]
- Mechanism of action: not known but thought to be similar to their underlying anticonvulsant effects- suppression of paroxysmal discharges and spread from the site of origin; reduction of neuronal hyperexcitability[175]
- Drug selection: no evidence to suggest superiority of one anticonvulsant over another
  - Many clinicians begin with gabapentin (good safety profile, favorable anecdotal experience) or carbamazepine (good response rate observed in trigeminal neuralgia)

TABLE 5.21 Adjuvant Analgesics Typically Selected For Neuropathic Pain with Predominating Lancinating ("Shooting") or Paroxysmal (Sudden Onset) Dysesthesias

Class	Examples
	Usually Tried First
Anticonvulsants	Carbamazepine, phenytoin, valproate, clonazepam
Baclofen	
	For Refractory Cases
Systemic local anesthetics	Mexiletine, tocainide, flecainide
Tricyclic antidepressants	See Table 5.15
"Newer" antidepressants	See Table 5.15
Neuroleptics	Pimozide
Alpha$_2$-adrenergic agonists	Clonidine
Topical agents	Capsaicin, local anesthetics
NMDA receptor antagonists	Dextromethorphan, ketamine
Calcitonin	

Adapted from McCaffery M, Pasero C: *Pain: Clinical manual*, p. 321. Copyright © 1999, Mosby, Inc.

TABLE 5.22 Commonly Used Adjuvant Analgesics

Drug Class	Indications	Preferred Drugs/ Routes	Usual Starting Dose (mg/day)	Usual Effective Dose Range	(mg/ day)	Dosing Schedule
Comments *Alpha$_2$-adrenergic agonist*	Multipurpose for chronic pain	Clonidine (Catapres +generics) PO	0.1	?	qd	Doses may be increased by 0. 1 mg/day q3-5 days
	Acute nociceptive pain or chronic neuropathic pain	Epidural	25 mcg/h	Same	q1h	Added to local anesthetics, clonidineprolongs anesthesia for surgery; combined with epidural opioids, it reduces the opioid dose required. Onset of side effects and analgesia within 30-60 min Epidural superior to IV
Anticonvulsants	First line for paroxysmal (sudden onset) or "shooting" neuropathic pain; second line for nonparoxysmal	Carbamazepine PO (Tegretol+ generics)	200	600-1200	q6-8h	increase in increments of 100mg every 2-3 days
		Clonazepam (Rivotril + generics) PO	0.5	0.5-3	q8h	
		Divalproex sodium PO (Epival+generics)	500	1500-3000	q8h	
		Phenytoin (Dilantin+ generics) PO	300	300	hs	Loading doses may be used (e.g. 500 mg X 2)
		IV	500-1000	?	?	IV dose used for rapidly escalating neuropathic pain
		Valproate sodium PO (Depakene+generics)	250	1500	hs to tid	increase in increments of 250mg every 2-3 days
	Multipurpose for all types of neuropathic pain	Gabapentin PO (Neurontin+ generics)	100-300	300-3600	q8h	May increase dose daily
Antidepressants Tricyclics	Multipurpose for chronic pain; effective for both continuous and" shooting" neuropathic pain, but generally used as second-line agents for paroxysmal (sudden onset) pain	Amitriptyline (Elavil + generics) PO	10-25	50-150	hs	Traditionally amitriptyline was first line. Because of side effects and recent evidence of comparable analgesia, desipramine is preferred for many patients, especially elderly. Less hypotension with nortriptyline. Evaluate and titrate upward q3-5 days. Some patients may prefer divided doses (e.g., q8h)
		Clomipramine PO (Anafranil + generics)	10-25	50-150	hs	
		Desipramine PO (Norpramin+generics)	10-25	50-150	hs	
		Doxepin (Sinequan + generics) PO	10-25	50-150	hs	
		Imipramine (Tofranil + generics) PO	10-25	50-150	hs	
		Nortriptyline (Aventyl + generics) PO	10-25	50-150	hs	

TABLE 5.22 Commonly Used Adjuvant Analgesics

Drug Class	Indications	Preferred Drugs/ Routes	Usual Starting Dose (mg/day)	Usual Effective Dose Range (mg/day)	Dosing Schedule	Comments
Antidepressants "Newer"	Same as above	Fluoxetine (Prozac + generics) PO	10-20	20-40	qd	Fewer side effects than tricyclics; less evidence of effectiveness
		Paroxetine (Paxil) PO	20	20-40	qd	
		Sertraline (Zoloft + generics) PO	50	150-200	qd	
Corticosteroids	Multipurpose analgesics	Dexamethasone PO (Decadron+generics)	Low-dose regimen: 1-2 mg	Same	qd or bid	May also improve appetite, nausea, and malaise. In patients with advanced medical illness, long-term treatment with low doses is generally well tolerated; used when pain persists after optimal opioid dosing.
			High-dose regimen: 100 mg then 96 mg in 4 divided doses		qid	High doses used for acute episode of severe pain unresponsive to opioids. Risk of serious toxicity increases with dose, duration of therapy, and coadministration of a NSAID
GABAergic	"Shooting" neuropathic pain	Baclofen (Lioresal + generics) PO	15	30-200	q8h	
Local anesthetics	Neuropathic pain of any type	Mexiletine (Mexitil + generics) PO	150	900-1200	q8h	Mexiletine is safer than tocainide and should be tried first. Plasma concentrations should be followed to reduce risk of toxicity
		Tocainide (Tonocard) PO	400	1200-1600	q8h	
NMDA Receptor Blockers	Refractory pain, second line choice	Ketamine (Ketalar) SC	40-150	240-480 continuous infusion		Subanesthetic doses for analgesia, patient remains alert. Careful monitoring, significant adverse effects- should be given by pain specialist only
		PO (injectable solution taken by mouth)	Same as IV	Same as IV	q6h	Efficacy equivalent to parenteral dose, despite limited bioavailability. Mix with orange juice to mask bitter taste
Neuroleptics	Pain associated with anxiety, restlessness, or nausea; multipurpose analgesic.	Methotrimeprazine PO (Nozinan + generics)	10	100	q6h	Side effects usually limit use to bedridden patients with advanced cancer. 10 mg approximately equal to 5 mg morphine.
	Trigeminal neuralgia; neuropathic pain	Pimozide (Orap) PO	2	4-12	q8h	Neuroleptic drug with side effects typical of this class (e.g., sedation)

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- Doses typically used for seizure control also used for adjuvant analgesic effect[176] (see Table 5.21)
- Adverse effects specific for each agent:
  - **Gabapentin** has a low side effect profile with sedation, dizziness, and nausea or GI upset as the only common adverse effects
  - **Carbamazepine** commonly causes sedation, dizziness, nausea, and unsteadiness; rarely causes serious leukopenia or thrombocytopenia, hepatic damage, hyponatremia from SIADH, or congestive heart failure
    - Complete blood count (CBC), and baseline liver and renal function tests before the start of therapy, then monitor CBC every three to four months
  - **Clonazepam** is a benzodiazepine drug, which most commonly causes sedation (additive to other sedating drugs); use limited by analgesic tolerance often develops within weeks of treatment[illegible]
  - **Phenytoin** side effects are mostly dose dependent at levels higher than typically used for seizure control or adjuvant analgesia (sedation or mental clouding, dizziness, unsteadiness, and diplopia)
  - **Valproate** side effects are usually mild, consisting of sedation, nausea, tremor, and sometimes increased appetite

Baclofen (GABA Agonist)

- Agonist at the GABA type B receptor
- Common second-line treatment for trigeminal neuralgia; also efficacious for lancinating or paroxysmal neuropathic pain[177-179]
- Dosing the same as for primary indication of spasticity- start at 5 mg two to three times per day, gradually escalated to 30 to 90 mg/day
- Adverse effects include dizziness, sedation, and gastrointestinal distress- minimized by gradual dose escalation; potential for a serious withdrawal syndrome including delirium and seizures

5.7.3 Refractory Cases Of Neuropathic Pain

Since neuropathic pain can be difficult to manage, first and second-line therapies may be ineffective. There are other options to consider if the neuropathic pain is refractory (see Tables 5.19 & 5.20)

N-Methyl-D-Aspartate (NMDA) Receptor Blockers: Dextromethorphan and Ketamine

NMDA receptor antagonists are under investigation as potential analgesics. Two commercially available drugs are NMDA receptor antagonists: the antitussive dextromethorphan (DM) and the general anesthetic ketamine. Dextromethorphan may be useful for the prevention of morphine tolerance or the enhancement of NSAID analgesia[180-182]. Ketamine has been used for neuropathic pain, including phantom limb pain[183-185]. Dosing suggestions for ketamine are outlined in Table 5.21.

In addition, the opioid methadone is considered to be an NMDA receptor blocker, and may act similar to these adjuvants as well as its central opioid actions.

Topical Analgesics (see Table 5.23)

- For neuropathic pain syndromes characterized by both a predominating peripheral mechanism and continuous dysesthesia
  - Most clinicians try capsaicin[186,187], although there are no comparative trials of the various topical therapies.
- Topical capsaicin:
  - Reduces pain by reducing the concentration of small peptides (including substance P) in primary afferent neurons[188]
  - Adverse effects are minimal- can cause local burning, which is sometimes intense, but does not cause tissue damage
- Topical antiinflammatory drugs:
  - Effectiveness for neuropathic pain remains unproven[189]
- Topical local anesthetics:
  - Commercially available mixture of local

anesthetics (contains a 1:1 mixture of prilocaine and lidocaine) capable of penetrating the skin and producing a dense local cutaneous anesthesia

- Product is known as eutectic mixture of local anesthetics (EMLA)[190]
- Used to prevent the pain of needle puncture or incision
- 5% lidocaine gel or patches for postherpetic neuralgia- significant decreases in pain and allodynia (pain cause by nonpainful stimuli such as touch), well tolerated with few side effects[192]

TABLE 5.23 Topical Analgesics

Type	Example
Topical capsaicin	Zostrix
Topical anti-inflammatory drugs	Aspirin in chloroform
Topical local anesthetics	EMLA, patches of 5% lidocaine

Adapted from McCaffery M, Pasero C: Pain: Clinical manual, p. 331. Copyright © 1999, Mosby, Inc.

Neuroleptics

- Some neuroleptics considered nonspecific multipurpose analgesics; evidence lacking for most agents in this class
  - Parenteral methotrimeprazine 10 to 20 mg is equianalgesic to morphine 10 mg IM[193-196]
  - Pimozide 4 to 12 mg PO per day has analgesic efficacy for treatment of trigeminal neuralgia[197]
- Mechanism of action: unknown, but may involve the effect of dopaminergic blockade (specifically at the D2 receptor subtype) on endogenous pain-modulating systems
- Indications: methotrimeprazine useful in bedridden patients with advanced cancer, who experience pain associated with anxiety, restlessness, or nausea (sedative, anxiolytic, & antiemetic effects favorable, and orthostatic hypotension is not a problem)
- Treatment often limited by extrapyramidal side effects, which include acute dystonic reactions (muscle contraction and jerking movements), akathisia (restlessness), parkinsonism, and tardive dyskinesia
  - Other adverse effects include sedation, orthostatic dizziness, anticholinergic effects, and sometimes mental clouding or confusion

5.8 Bone Pain

When bone involvement is suspected in a cancer patient, diagnosic imaging should be considered to set a baseline and to detect early stages of bone metastases. Prophylactic subluxation may be considered before advanced disease causes bones to break. Non-pharmacologic interventions must be included in the management strategy, along with the use of drug therapy including corticosteroids, NSAIDs, biphosphonates (osteoclast inhibitor to reduce bone resorption (e.g. pamidronate)), and radiopharmaceuticals (strontium-89 and samarium-153)[126-129], as listed in Table 5.24. Other pain syndrome may be experienced concurrently with bone pain, and all types of pain should be managed at the same time. Other dimensions of total pain and suffering may benefit from psychosocial and spiritual support, especially if drugs and physical interventions are not completely effective.

Choice of drug

- The type of pain being treated determines the choice of drug group
- Within each drug group, selection is made on the basis of multiple patient characteristics, such as age and other medical conditions.
- If one adjuvant is ineffective or causes unacceptable and unmanageable side effects, another adjuvant analgesic in that drug group or in another group should be used. Individuals vary in their responses to these drugs.
- Some drugs may require referral to a specialist for administration (e.g. radiopharmaceuticals by nuclear medicine department)

Routes and dosing

- Almost all adjuvant analgesics are available orally; some may be given parenterally.
- Generally a ceiling effect for bone pain exists on the analgesia of adjuvants
- Some agents have a prolonged effect (e.g. biphosphonates, radiopharmaceuticals); others require continuous dosing (e.g. non-steroidal anti-inflammatory drugs, steroids)
- Some continuously dosed agents may be titrated upward slowly; analgesia is delayed until the appropriate dose is reached and the drug accumulates.
- The maximum analgesic effect may not occur for several days or longer.

Bisphosphonates

- Analogs of inorganic pyrophosphate that inhibit osteoclast activity and reduce bone resorption[126-129, 199]
- Pamidronate 60 mg every two to four weeks (to 90 mg every 4 weeks)[200] provides at least partial bone pain relief in 50% of patients, and pain-free in almost one third
  - Onset of analgesia takes several weeks after treatment (sometimes as early as 2 weeks); several doses are needed for full efficacy
- Bisphosphonates are most often administered in a chemotherapy program at the local hospital outpatient department- consider a referral to an oncologist or pain specialist[201-207]

TABLE 5.24 Adjuvant Analgesics Used for Malignant Bone Pain

Class	Comment
Bisphosphonates (e.g. pamidronate, zoledronic acid)	Reduces malignant bone pain and risk of skeletal morbidity
Radionuclides (e.g., strontium-89, samarium-153, gallium nitrate)	Slow onset, used only if no further chemotherapy is planned
Corticosteroids	Anecdotal reports of effectiveness in bone pain
NSAIDs	Anecdotal reports of effectiveness in bone pain
Calcitonin (not recommended)	Decreases rate of bone turnover; useful in osteoporosis; available IM, subcutaneous, and as nasal spray; evidence that calcitonin does not reduce bone pain

Adapted from McCaffery M, Pasero C: *Pain: Clinical manual*, p. 325. Copyright © 1999, Mosby, Inc.

Radiopharmaceuticals

- Radionuclides absorbed at areas of high bone turnover are potential therapies for metastatic bone cancer
- Newer radionuclides are potential therapies for bone pain (e.g. strontium chloride-89, samarium-153, and rhenium-186)
- Strontium-89 results in multifocal bone pain relief occurs in approximately 80% of patients; 10% complete relief- initial response occurs in 7 to 21 days, peak response may be delayed for a month or more, and the usual duration of benefit is 3 to 6 months[208-209]
  - Clinically significant leukopenia or thrombocytopenia occurs in approximately 10% and 33% of patients
- Radionuclides must be administered by a licenced nuclear medicine department, and are very expensive per dose

Non-Pharmacological Management

Pain from bone metastases of cancer may also be managed by non-drug approaches:

- Radiotherapy is often used for short to long-term management; referral to radiation oncology is required, but responses may be durable without significant side effects
- Surgical fixation may be indicated for unstable bones or joints associated with bone pain
- Physiotherapy may also be an effective option for pain reduction, although there may be incident pain during manipulations

Calcitonin

- Calcitonin is relatively safe and early studies suggested that it could occasionally relieve bone pain[126,127,129,198]; however, recent evidence has not shown effectiveness in the reduction of bone pain, and calcitonin is no longer recommended for management of bone pain[210]

5.9 Incident Pain

Incident pain is a type of breakthrough pain that is made worse by movement. This is more common in patients with advanced cancer, or with bone pain, and may become predictable. Incident pain may be expected when a partially-bedridden patient is mobilized, or during physiotherapy activities. If possible, incident pain should be managed as much as possible with non-pharmacologic interventions before drug therapy is initiated. Health care professionals should carefully assess the cause of incident pain, and plan for preventive management where possible.

Pharmacologic management of incident pain involves the use of short-acting analgesics, administered in advance of the pain-causing activity. Ideally, the drug will reach its onset of action by the time the painful event begins, then dissipate shortly after the event is over. The usual BTP dose may be used, but may extend beyond the time needed.

Short-acting opioids for incident pain include fentanyl 200 mcg SL/buccal, or its derivative, sufentanil 5-50 mcg SL/buccal. Another option is the use of ketamine 0.125-1 mg/Kg SC, which also has a rapid onset and short duration of action with a single dose.

5.10 Pain from compression or distension of tissues

- Tumour may compress or distend visceral tissues, leading to profound local pain
- Local treatment is first-line option, where possible: surgical decompression, radiotherapy
- Corticosteroid may be used for short-term control (e.g. for weeks while waiting for onset of radiotherapy effect), or long-term (if local therapy not possible or ineffective)
  - Dexamethasone 4 mg PO qAM (may use higher or lower doses)
  - May be added to NSAID/ Acetaminophen, or replace NSAID
  - Plan use for limited period, monitor for effects; taper dose to discontinue
- Symptoms associated with malignant bowel obstruction (e.g. distension pain, nausea & vomiting): surgical decompression if feasible; anticholinergic drugs (e.g. transdermal scopolamine), the somatostatin analog octreotide[211,212], or corticosteroids

5.11 Non-pharmacological management

Although the discussion so far has concentrated upon the many aspects of interventional pharmacotherapy, there are many non-pharmacologic approaches to pain management. Several of these approaches are illustrated in Table 5.25.

Cancer patients often experience many different types and dimensions of pain at the same time. A comprehensive pain management strategy should be built upon a thorough pain assessment, including all aspects of total pain, and include different combinations of managment interventions, appropriate to individual patient needs. For instance, optimal pharmacotherapy may fail if a patient is overwhelmed by psychosocial or spiritual suffering. Complex pain problems may require complex management plans.

Table 5.25 Non-Pharmacologic Interventions for Cancer Pain Management

Method	Benefit for Pain
	1. Psycho-social-spiritual Interventions
Patient Education	• promotes self care in pain treatment and management of side effects
Patient Counselling	• may improve patient's coping skills and provide emotional comfort • facilitates communication
Family Counselling	• may alleviate stress within the family and facilitate communication between patient and family
Life Review	• reinforces social and spiritual value of their life and self worth
Recreational Activities	• increase pain threshold through distraction
Relaxation Therapy Imagery	• may reduce pain and anxiety through distraction/relaxation • examples include: music, guided imagery, visualization
Social Interactions	• reduces fears, anxieties, boredom/isolation • promotes self awareness, social contact • stimulates communication
Spiritual Counselling	• may improve patient's coping skills and provide spiritual and emotional comfort
	2. Physical Interventions
Cutaneous Stimulation-Heat/Cold	• reduction in swelling • examples: wax, packs, magic bags, ice*
Massage*	• relaxation • reduction in swelling, relaxation
Mechanical Aids- TENS/ Acupressure/Vibrators	• promotes relaxation • stimulates known pressure points/nerves
Laser/Ultrasound	• may reduce pain related to inflammation or spasm • promotes healing
Therapeutic Touch	• promotes relaxation and well being by utilization of body's electro-mechanical energy field
Positioning Strategies	• enhance comfort function and reduce pressure sore development
Movement (active, active-assisted, passive)	• prevent deformity, reduces spasticity, maintains or improves joint mobility, improves circulation and preserves skin integrity
Orthotics (splints, slings, lower extremity braces)	• improve comfort while enhancing function
	3. Other
Radiation Therapy	• directly treats tumours (especially helpful for bone metastases) • reduce opioid dose, to compensate for analgesia from radiotherapy
Regional Neurolytic Block or Spinal Epidural Anesthesia	• can benefit pain refractory to drug therapy or when drug therapy causes intolerable or intractable side effects • reduce analgesic drug(s) dosage for localized pain, reduce side effects
Neurosurgery- Dorsal root entry zone (DREZ), dorsal rhizotomy, cordotomy	• can control pain when drug therapy causes intolerable or intractable side effects or cannot provide adequate pain control
Surgery (eg. Orthopaedic, GI)	• treats underlying cause for pain specifically (e.g. fracture, bowel obstruction).

* *Volunteer and family may continue intervention after initial assessment by physiotherapist to ensure no contraindications.*

5.12 Special Pain Problems

5.12.1 Pain Crisis

Pain crisis is acute severe pain which is overwhelming and exceeds the coping strategies of the patient and family. Pain crisis may occur with any patient at any point in time. As a crisis, there is no time for the usual dose titration. Pain crisis is an **emergency** situation.

The management of pain crisis involves an urgent visit for assessment and initiation of treatment, as illustrated in Figure 5.9. Since the patient is in crisis, it is important to manage both the pain and the distress. For example, the total daily opioid dose may be increased by 25-50% and given as the equivalent parenteral dose (for rapid dosing), along with lorazepam 0.5-1 mg SC or midazolam 1mg (up to 5 mg) SC for immediate distress management. This may be repeated every 30 minutes for three doses or until pain relief or sedation. If available, a palliative care or pain specialist should be involved in this care.

Caution is required during this aggressive treatment, to avoid excessive sedation and respiratory depression. Monitor the respiratory rate, and SaO_2 (if available). If there is respiratory depression with low O_2 saturation, administer oxygen, and provide verbal & tactile stimulation; if response is inadequate, consider giving low dose naloxone (0.4 mg diluted in saline to 10 mL, give 1 mL q1-2 minutes until adequate SaO_2 level). It may be necessary to hospitalize this patient during or following the pain crisis management.

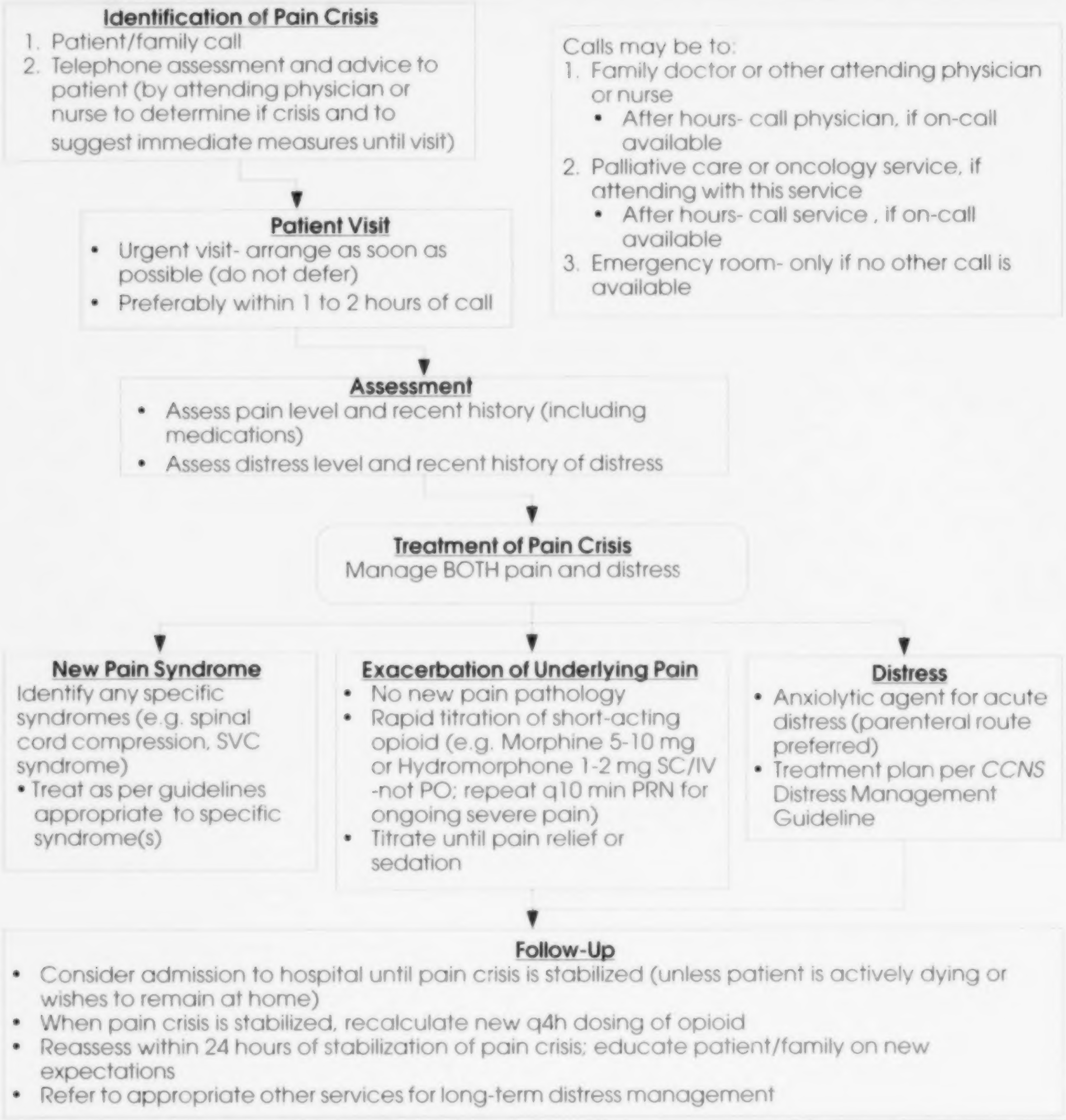
5.12.2 Refractory Pain & Palliative Sedation

Refractory pain is pain that is **not** adequately controlled despite aggressive efforts to identify and provide a tolerable therapy in a timely fashion, that does not compromise consciousness. This is pain that is intolerable, unbearable and intractible. Refractory pain must be distingushed from difficult pain, which is pain that has not been managed with usual efforts and requires aggressive intensive efforts for a timely effect.

The challenge of managing refratory pain is in the decision to use palliative sedation. Key steps are outlined in Figure 5.10. A very careful assessment must identify that all reasonable efforts to control the pain by other means have been exhausted, and that the patient has a short life expectancy. No health care professional should attempt palliative sedation by themselves- this requires a team effort, often including an ethics team. A truly informed consent is required before palliative sedation begins. Once started, the physician or nurse must monitor pain and consciousness regularly, and adjust doses as needed.

Options for Palliative Sedation-
- Start at low dose and titrate to effect
- Midazolam 1-7 mg/hr SC/IV infusion
- Lorazepam 1-4 mg SC q4-6h
- Methotrimeprazine 5-25 mg SC q4h (only option with analgesic effects)
- Haloperidol 2-10 mg SC q4h
- Propofol 0.5-7 mg/hr IV infusion (NB. general anesthetic with rapid onset and elimination- may be restricted in some hospitals)
- May add breakthrough doses of same drug as needed

Figure 5.9 Management of a Pain Crisis



Identification of Pain Crisis

1. Patient/family call
2. Telephone assessment and advice to patient (by attending physician or nurse to determine if crisis and to suggest immediate measures until visit)

Calls may be to:

1. Family doctor or other attending physician or nurse
   - After hours- call physician, if on-call available
2. Palliative care or oncology service, if attending with this service
   - After hours- call service , if on-call available
3. Emergency room- only if no other call is available

Patient Visit

- Urgent visit- arrange as soon as possible (do not defer)
- Preferably within 1 to 2 hours of call

Assessment

- Assess pain level and recent history (including medications)
- Assess distress level and recent history of distress

Treatment of Pain Crisis

Manage BOTH pain and distress

New Pain Syndrome

Identify any specific syndromes (e.g. spinal cord compression, SVC syndrome)

- Treat as per guidelines appropriate to specific syndrome(s)

Exacerbation of Underlying Pain

- No new pain pathology
- Rapid titration of short-acting opioid (e.g. Morphine 5-10 mg or Hydromorphone 1-2 mg SC/IV -not PO; repeat q10 min PRN for ongoing severe pain)
- Titrate until pain relief or sedation

Distress

- Anxiolytic agent for acute distress (parenteral route preferred)
- Treatment plan per *CCNS* Distress Management Guideline

Follow-Up

- Consider admission to hospital until pain crisis is stabilized (unless patient is actively dying or wishes to remain at home)
- When pain crisis is stabilized, recalculate new q4h dosing of opioid
- Reassess within 24 hours of stabilization of pain crisis; educate patient/family on new expectations
- Refer to appropriate other services for long-term distress management

May be duplicated for use in clinical practice. As appears in: Broadfield L, Banerjee S, Jewers H, Pollett AJ, Simpson J., Guidelines for the Management of Cancer-Related Pain in Adults. © *Cancer Care Nova Scotia*, 2005

Figure 5.10 Palliative Sedation for Refractory Pain

Identify Refractory Pain by the Health Care Professional

- Patient continues to report ongoing, intolerable pain despite aggressive therapy
- Differential diagnosis to exclude difficult pain syndrome
- All efforts to control pain have been adequately explored
- Pain control efforts that cannot be achieved within a reasonable time, relative to the patient's prognosis and expectations, are ruled out

▼

Assessment of Refractory Pain

- Use assessment tools for cancer pain (see Assessment of Cancer Pain); increase frequency of assessments
- Consult with other sub-specialists to ensure that all reasonable efforts to manage pain have been taken

▼

Decision to Offer Palliative Sedation

- Involve the patient/family, the interdisciplinary team and, if necessary, the ethics team
- Palliative sedation should ONLY by offered by a consultation service, or a team which includes at least two physicians; other disciplines (e.g. nursing, spiritual care, social work) will be involved during treatment
- Review the ethics of palliative sedation with the patient/family, including the seriousness of the prognosis, the lack of alternative options for pain relief, short life expectancy, and the intention is to relieve suffering/pain but not to hasten death
    - Consultation by an ethics committee is recommended when there is conflict about the decision
- Explain all treatment options to the patient/family, negotiate the terms of sedation (e.g. continuous, intermittent, periodic, on demand)
- **Obtain informed patient consent** (or surrogate, only if the patient is incompetent); document on the health record

▼

Management of Palliative Sedation

- Select a treatment option, which is available for the treatment setting
- Monitor patient's pain, respiratory rate and consciousness regularly; review with physician at least every 24 hours
- Physician to titrate sedative medications to meet the treatment goals, do not order dose ranges
- Maintain previous opioid therapy (may be able to reduce dosage)

May be duplicated for use in clinical practice. As appears in: Broadfield L, Banerjee S, Jewers H, Pollett AJ, Simpson J. Guidelines for the Management of Cancer-Related Pain in Adults. © *Cancer Care Nova Scotia*, 2005

5.12.3 Pain Treatment in Substance Abusers

Another challenge in cancer pain management is the cancer patient who is known or suspected to be a substance abuser. These patients, or their family and friends, are potential abusers of the analgesic medications, particularly opioids. They may also divert drugs for trafficking or other illicit purposes. Prescribers are reluctant to issue opioid prescriptions, yet their pain needs management like any other cancer patient.

The key to this patient group is behaviour management with careful assessment and monitoring, as illustrated in Figure 5.11. If the prescriber is uncertain about care of these patients, consider consult to an appropriate specialist (eg. palliative care / pain specialist, in collaboration with drug dependency service).

The assessment should include routine screening (e.g. CAGE questionnaire), as well as a careful examination for physical signs indicative of substance abuse behaviour. If abuse is identified, or still suspected despite lack of findings, the prescriber should negotiate and enforce a treatment contract with the patient (see Form 8.5- Sample agreement for opioid therapy).

Figure 5.11 Strategy for Pain Management in Known or Suspected Substance Abusers

Identify Patients at High Risk of Substance Abuse

▼

Assessment

- In addition to usual pain assessment consider a thorough history to include:
  - Alcohol, drugs and tobacco use (consider CAGE Questionnaire)
  - Compulsive behaviors (e.g. gambling)
  - Mental health issues
  - Social supports or systems
  - Previous criminal record (patient and family)
- Correlation to physical exam results
- Consider drug screening tests

▼

Pain Treatment

- Treat the cancer pain
- Higher doses of opioids will be necessary for cancer pain control in patients who are substance abusers
- Consider using methadone or fentanyl patches, optimize adjuvants
- Develop a contract with the patient (see Form 8.5)
- Compliance monitoring crucial
- Consider prescribing small supplies or daily supply of opioids, notification of pharmacies and narcotic monitoring system
- Consider use of tamper-proof medication containers
- Consider unplanned visits to screen for drug use (include in contract)
- Report to police any questionable activities (which could be drug diversion)

▼

Follow-up Practices

- Regular follow-up visits to ensure compliance with contract
- Ensure pain relief is addressed

May be duplicated for use in clinical practice. As appears in: Broadfield L, Banerjee S, Jewers H, Pollett AJ, Simpson J. Guidelines for the Management of Cancer-Related Pain in Adults. © *Cancer Care Nova Scotia*, 2005

Inappropriate drug-seeking behaviours must be recognized and prospectively managed. Collaboration with the retail pharmacy and other physicians in the practice group (as well as the involved specialists) will reinforce the agreement and prevent double-doctoring and other drug diversion activities.

Opioids which minimize abuse potential, such as methadone or transdermal fentanyl patches may be used. Nonopioids and adjuvants should be considered, to reduce the amount of opioid required by the patient.

There must be real consequence to noncompliance with the agreement, which may include withdrawal of prescribing and involvement of police, if necessary. If the patient does not believe in the consequences, compliance with the agreement is at risk. Despite the best management plan, however, some substance abusers will find a way to trick prescribers into prescribing and pharmacists into dispensing opioids.

5.12.4 Spasms or cramps

For muscular or skeletal spasms:

- Baclofen 5 mg PO TID (may titrate q3d up to 20 mg PO TID)[illegible]
- Diazepam 2 mg PO TID (may titrate up to 10 mg PO TID
- Midazolam 1-3 mg SC q30 min PRN (or lorazepam 0.5-2 mg SC q1 hr PRN)

For visceral spasms or cramps:

- Loperamide 1-2 mg PO TID to QID
- Buscopan (hyoscine butylbromide) 10 mg PO TID-QID
- Scopolamine transdermal patch 1.5 mg q3d
- Glycopyrrolate 0.2-0.4 mg SC q4-8h
- Consider Octreotide 200 mcg SC q8h (may increase to 800 mcg)[illegible]

5.12.5 Post-radiation pain

Acute Pain Problems (e.g. burns):

- Most radiation-induced pain responds to usual opioid therapy; see Section 5.5
- If severe, consult with radiation oncologist for management

Pain Flares

- Rapid upward titration of opioid when pain increases
- Careful monitoring, decrease opioids when pain decreases

5.12.6 Chemotherapy-related pain syndromes

Drug-Related Neuropathies:

- Consult with oncologist (chemotherapy may be altered)
- Treatment like neuropathic pain (see Section 5.6.1)
- Educate patient/family
- Explore psychosocial support groups, complementary treatment options

Hand-Foot Syndrome (Palmar-Plantar Erythrodysaesthesia or PPE):

- Consult with oncologist (chemotherapy may be altered)
- Symptomatic relief with topical moisturizing creams (e.g. BagBalm, Udder Cream)

Mucositis Pain:

- Use a "stepped" approach for mucositis management, with progression from one level to the next as follows:
  1. Mucosal coating agents (e.g., antacid or kaolin suspensions)
  2. Water-soluble lubricating agents, including artificial saliva for xerostomia
  3. Topical anesthetics (e.g., viscous lidocaine, benzocaine sprays/gels, benzydamine rinse, diphenhydramine solutions)
- May combine ingredients into a standard pain relief mouthwash preparation
- For more information, see **CCNS Guidelines for the Management of Oral Complications from Cancer Therapy**

Table 5.26 Cancer-Related Pain Syndromes

Syndrome	Pain Characteristics	Comments
	Musculoskeletal Tumour Involvement	
General bony involvement:	• presents as sharp, throbbing, achy, or pressure-like pain in long bones, shoulder, pelvis, hip	• often localized- consider local therapy (e.g. radiotherapy) • worsened by movement, weight-bearing
First Cervical Vertebra (Base of skull):	• presents as sharp neck pain • may radiate to posterior skull, some sensory/motor loss in upper extremities	• associated with multiple myeloma, bone metastases from breast cancer
Chest Wall:	• local pain- sharp, throbbing, achy, or pressure-like	• hyperalgesia in some patients • infiltration from breast or lung cancer
	Visceral Tumour Involvement	
Abdomen:	• presents as cramping pain	• may radiate to groin, shoulder, back, retroperitoneum
Intestinal Obstruction:	• colicky, cramping, dull aching pain • manage symptoms as appropriate	• may be accompanied by distension, ascites, diarrhea, constipation, nausea, vomiting, and bowel obstruction
	Peripheral or Central Nervous System Involvement (Neuropathic Pain)	
Ribs/intercostal Nerves:	• burning, shooting, shock-like pain which radiates along nerve root • tumour infiltration of peripheral nerves	• may be worsened by deep breathing, chest movement • possible sensory loss distal to area of nerve compression
Brachial Plexus:	• burning, shooting, shock-like pain in shoulder, radiating down arm • consider CT/MRI to evaluate plexus • tumour infiltration or compression of plexus	• may experience numbness, paresthesias (burning, tingling), hyperalgesia, and allodynia • consider local radiotherapy
Lumbar Plexus:	• burning, shooting, shock-like, achy, pressure-like pain in thigh or groin • compression from local extension of lymph node metastases	• numbness (not relieved by analgesics), paresthesias, weakness, or leg edema
Sacral Plexus:	• burning, shooting, shock-like, dull, achy pain in midline of lower back	• associated with genitourinary, gynecologic and colon cancers • perianal sensory loss, difficulty sitting, impotency, bowel and bladder dysfunction
Spinal Cord:	• dull, aching, sharp with movement, tight, bandlike pain in neck (cervical vertebrae), upper back (thoracic vertebrae), or lower back (lumbar vertebrae)- general or localized pain • spinal cord compression following metastasis to vertebral bones, direct effect from tumour (e.g.myeloma)	• leads to epidural spinal cord compression (ESCC)- **oncologic emergency** --> urgent radiotherapy • untreated ESCC can result in paraplegia or quadriplegia; can progress rapidly from pain to sensory loss to motor loss to loss of bowel or bladder control
	Postsurgical Pain	
Postmastectomy, Postthoracotomy:	• tight, constricting, burning, aching pain in posterior arm & axilla (mastectomy) or chest wall • may include neuropathic pain symptoms	• begins 1-2 months after surgery • worse with movement; may lead to frozen shoulder • recurrent pain in thoracotomy scar area may indicate recurrent tumour

Corticosteroid-Associated Pain:

- Tenderness/aching in muscles and joints may be related to taper of steroids-reinstitute steroid and taper more gradually
- Aseptic necrosis of femoral or humoral head from chronic steroid use; gradual taper of steroid, may require joint replacement

5.12.7 Chronic Pain in Cancer Patients:

- Cancer patients may also suffer from pain due to other causes
- Treat each type of pain, as appropriate
- Pain may be due to cancer treatment (e.g. surgery, radiation therapy)
- Consider referral to appropriate sub-specialist (e.g. gastroenterology, neurology, urology, ENT), or pain specialist
- Consider non-pharmcological approaches (e.g. physiotherapy, nerve blocks, TENS, distraction methods, guided imagery)
- Consider appropriate support groups

5.12.8 Cancer-Related Pain Syndromes

There are three main types of pain experienced by cancer patients:

1. direct cancer pain from tumour involvement- included local, regional, and metastatic cancers (65-85% of cancer patients)
2. Pain from cancer-related procedures-surgery, radiotherapy, chemotherapy (see Sections 5.8.5, 5.8.6 and Table 5.26) (15-25% of cancer patients)
3. Pain from causes unrelated to the cancer (e.g. chronic low back pain, rheumatoid arthritis) (3-10% of cancer patients)

- May have 2 or 3 types of pain at the same time
- Acute pain syndromes may be superimposed on background chronic pain
- Pain syndromes may be nociceptive, neuropathic, or both
- There are also distinct cancer pain syndromes (Table 5.26), related to the anatomic areas of tumour involvement

5.13 Special populations

5.13.1 *Cognitively-impaired patients*

Cognitive impairment can be a barrier to effective assessment and management of pain. The patient may be temporarily cognitively-impaired as a result of their acute pain episode, or may be more permanently impaired as a comorbidity. Cognitive impairment is most common in elderly patients. Although opioids are sedating, there is no evidence that these agents induce cognitive impairment. In fact, it is poorly controlled pain that has been shown to contribute to cognitive impairment in post-operative patients, and effective analgesic use has reduced the impairment. Some NSAIDs may induce cognitive impairment.

Self-assessment of pain by a cognitively-impaired patient has not been proven less valid than assessment by an intact patient. Given sufficient time to process information and respond, a cognitively-impaired patient can provide an accurate self-assessment, although this group of patients prefer the simpler 0-5 scale with word anchors.

Therefore, one should rely upon patient self-assessment of pain, but allow the cognitively-impaired patient adequate time to understand and respond to the pain intensity scale. There is no reason to withhold opioid analgesics in a cognitively-impaired patient, although NSAIDs and other coanalgesics should be considered with more caution.

5.13.2 *Pain & Depression*

Anxiety and depression may be a normal response by the patient to uncontrolled pain. Psychiatric disorders, including depression, are more common in cancer patients with pain than in those without pain. There is not sufficient evidence to conclude that pain is experienced differently in a patient with underlying clinical depression. Depression does not appear to influence the self-assessment of pain intensity, even if the depression is a result of the pain.

Effective pain management should not be withheld or diminshed in patients who are depressed. Rather, all reasonable effort should be made to reduce or eliminate pain as a method to also reduce depression. Pharmacotherapeutic measures may include both analgesics and antidepressants, and may be combined with supportive psychotherapy and cognitive-behavioural skills training by the psychology or psychiatry specialists for optimal co-management of the pain and the depression.

5.13.3 Pain in the Elderly

Elderly patients may present additional challenges in the management of pain. Assessment of pain in the elderly is no different than any other group of patients, and clinicians must take their time to achieve good self-reports of pain, even in those elderly patients who are cognitively-impaired. The Faces Scale may be considered for those patients who cannot easily verbalize or react to numbers and written descriptors.

Pain management in the elderly may be complicated by impaired pharmacokinetic handling of drugs in these patients. Reduced organ capacities can alter the absorption, distribution, metabolism and elimination of certain drugs. Caution must be used when giving any drug with active or toxic metabolites, since these may accumulate more in an elderly patient with poor renal or hepatic function. NSAIDs must be used with care to avoid the increased risk of GI irritation and ulceration. Opioid analgesics do not diminish in analgesic effectiveness, but morphine may appear to be more toxic if the active metabolite accumulates in patients with impaired renal function. Hydromorphone or transdermal fentanyl may be better options for opioid agents. Meperidine should NOT be used in elderly patients.

Other than adjusting pharmacotherapy to accomodate reduced organ function and being patient with the assessment of pain, there is no reason to treat an elderly patient any different than a younger patient.

5.13.4 Pain in Children

This guideline does not address the special issues of pain management in children. It is recommended that the pediatric pain team, the pediatric palliative care team, or the pediatric hematologist-oncologist as appropriate be contacted for advice on specific patient management issues.

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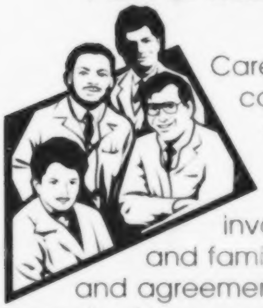
Part 6. Multidisciplinary Care of Patients with Cancer Pain-Implications for Practice



Care of the patient with cancer pain requires the efforts of a team of health care professionals and involvement of the patient and family. Open communication and agreement on the principles and goals of therapy are key ingredients for successful management of the pain. Common principles for pain control are outlined in Table 6.1. Care is individualized for each patient, based upon their physical status, the type of pain, and individual preferences and experiences (see Table 5.8).

6.1 Identification and Assessment

Care begins with the identification of pain in a cancer patient. These patients should be assessed on a regular basis for a variety of physical and psycho-social-emotional needs. Cancer patients require many dimensions of care during their journey through diagnosis, decision-making, treatment and follow-up. Since pain is a common symptom for cancer patients, screening to identify pain should be a routine component of ongoing care. Pain screening may be done by cancer specialists, family doctors, or any other health care professional involved with care of the cancer patient.

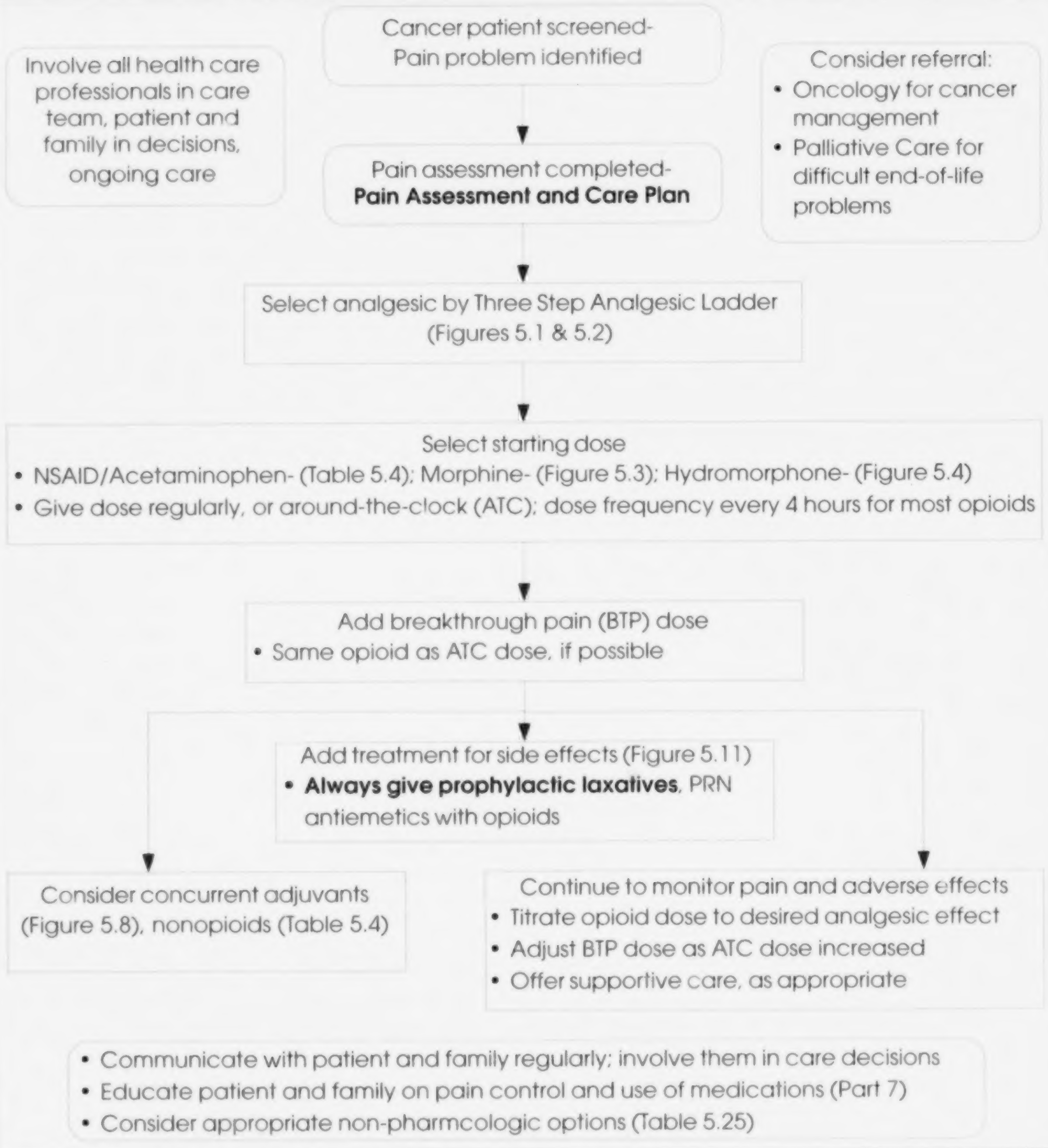
Once pain has been identified, a thorough assessment is required. This should not be delayed, since cancer pain may be serious and can escalate quickly in some patients. Pain assessment may require input from different health care professionals, and should certainly include a medical examination. Assessment information may travel with the patient and family, between institutions and community care and between treatment sites. Therefore, a common assessment form, the **Pain Assessment and Care Plan** (PACP) is recommended by *Cancer Care Nova Scotia* for use in all sites across Nova Scotia and by all health professionals when pain is a focus of care. This single form will standardize pain assessment and should improve communication about the pain problem(s) and care plan(s). It may be used in hospital (often with each nursing shift) or office practice, and is clearly intended for documentation by different health care professionals on the same form. In addition, documentation of ongoing monitoring is standardized on another common form, the **Pain Management Flowsheet**, also recommended by *Cancer Care Nova Scotia* for use in all locations and by all health care professionals. See Part 8 Documentation for more details and sample copies of the standard forms.

Table 6.1 Twelve Basic Principles of Pain Control

1. Always remember the concept of "total pain"
2. Do a thorough but reasonably rapid assessment of the pain
3. Avoid unnecessary delay in treating the pain, especially if it is severe
4. Educate the patient, family and other caregivers, and involve them in the pain treatment plan
5. Follow a stepped approach to analgesia that depends on the severity of the pain
6. Consider the use of adjuvant therapy at all stages
7. Give medication by mouth whenever possible
8. Constant pain requires regular administration of analgesics to maintain constant levels of analgesia
9. Always leave instructions for a "breakthrough" dose
10. Monitor the patient frequently and remain in communication
11. Treat other symptoms, such as constipation, nausea and muscle spasms aggressively
12. Be flexible

Adapted from Librach LS: *The Pain Manual*. Copyright © 1991. Pegasus Healthcare

Figure 6.1 Stepwise Management of Cancer Pain



Involve all health care professionals in care team, patient and family in decisions, ongoing care

Cancer patient screened- Pain problem identified

Consider referral:
- Oncology for cancer management
- Palliative Care for difficult end-of-life problems

Pain assessment completed- **Pain Assessment and Care Plan**

Select analgesic by Three Step Analgesic Ladder (Figures 5.1 & 5.2)

Select starting dose
- NSAID/Acetaminophen- (Table 5.4); Morphine- (Figure 5.3); Hydromorphone- (Figure 5.4)
- Give dose regularly, or around-the-clock (ATC); dose frequency every 4 hours for most opioids

Add breakthrough pain (BTP) dose
- Same opioid as ATC dose, if possible

Add treatment for side effects (Figure 5.11)
- **Always give prophylactic laxatives**, PRN antiemetics with opioids

Consider concurrent adjuvants (Figure 5.8), nonopioids (Table 5.4)

Continue to monitor pain and adverse effects
- Titrate opioid dose to desired analgesic effect
- Adjust BTP dose as ATC dose increased
- Offer supportive care, as appropriate

- Communicate with patient and family regularly; involve them in care decisions
- Educate patient and family on pain control and use of medications (Part 7)
- Consider appropriate non-pharmcologic options (Table 5.25)

May be duplicated for use in clinical practice. As appears in: Broadfield L, Banerjee S, Jewers H, Pollett AJ, Simpson J., Guidelines for the Management of Cancer-Related Pain in Adults. © *Cancer Care Nova Scotia*, 2005

health care professionals. See Part 8 Documentation for more details and sample copies of the standard forms.

6.2 Prescribing analgesics

Drug therapy is the foundation for cancer pain management, but prescribing opioids and other drugs is a continuing effort. A simplified stepwise approach is illustrated in Figure 6.1. Drug therapy must be individualized for each patient and adjusted over time as the pain changes. The prescriber should understand the pharmacology and dosing of the drugs being used (see Part 5 Management of Cancer-Related Pain). Misconceptions about opioid drugs persist, despite decades of training in cancer pain management. Prescribers and other health professionals involved in cancer patient care should be aware of their fears and concerns. A team approach to pain management may help to address some concerns and to resolve barriers to effective patient care.

Opioids are classified as narcotic agents and require compliance with the laws and regulations governing narcotic agents. This includes the use of triplicate prescriptiopn forms and new written prescriptions instead of refills (for some drugs). Involvement and communication with the retail pharmacist may help facilitate timely drug dispensing and prevent operational delays due to regulatory rules.

6.3 Polypharmacy

In other areas, it is preferable to limit the number of drugs used to manage a patient problem. For cancer pain, however, **the use of multiple drugs is desirable**. Nonopioids and adjuvants may be useful analgesics, and may help to reduce the opioid dose needed. Higher opioid doses are associated with more significant adverse effects, so lower doses are preferred. Some drugs, such as laxatives, should be given routinely to prevent opioid side effects.

When using multiple drugs, one must always be aware of the risk of drug interactions. Careful drug selection and regular monitoring must be the rules for polypharmacy. Keep in mind that patients are often on other drugs for different indications at the same time, further complicating the multiple drug therapies. If an unexpected adverse effect occurs, consider the possibility that it may be an interaction. The pharmacist may be helpful in identifying interactions.

6.4 Education

Another key ingredient to successful pain management is patient and family education (see Part 7). It is the responsibility of all health care professionals to educate patients and families. Good team communication is important, to ensure that the messages are not contradictory, and that important material is taught to the patient, and, where appropriate, reinforced by other professionals. Never assume that the patient understands all the information after a single teaching session- continual reinforcement is needed by many patients and families, especially as the pain changes.

6.5 Teamwork

Cancer pain patients have many needs. It takes a dedicated team to address these needs. Although the typical team starts with the doctor and nurse, many other health professionals can help the patient. The pharmacist can help with medication-related issues. The social worker, clergy, psychologist, and other counsellors may be involved for psychosocial supportive care. Occupational therapist and physiotherapist may be important team members for some patients. Specialists may already be involved in patient care, or may be needed on referral for specific interventions. Many other caregivers, professionals and volunteers can be helpful. The team may be as unique as the needs of each individual patient.

Clear communication is imperative as different people are involved in the care team. Most important is the involvement of the patient and family in the care team.

6.6 Follow-up

Cancer pain is not usually stable forever, and it does not usually go away. Patients must be followed over time by the team, or individual members as necessary. The pain must continue to be monitored and medications are frequently adjusted. It is important that the core team members follow the patient through their journey and that care does not become fractionated or discontinuous.

6.7 Dealing with difficult situations

Not all patients are easy to deal with. Some patients can pose challenges for the health care professional to manage. Cancer patients who are known or suspected substance abusers may require careful negotiation over care parameters (see Section 5.8.3). Cognitively-impaired patients (Section 5.9.1) and depressed patients (Section 5.9.2) may also be difficult for the health care professionals.

Teamwork may help with management of problem patients, but the team should also be prepared to call in other members or consultants, if the problem(s) demand different expertise.

6.8 Issues at end of life

Finally, pain is part of the disease experience as cancer progresses to the end of life. Palliative care expertise can be very useful through cancer pain management, and especially at end of life. Teamwork is particularly important as other symptoms and end of life issues complicate patient care.

Part 7. Patient and Family Education

Involving the patient and family in the plan of care is a fundamental principle of pain management. Patients and families are active participants in their own care, and should be encouraged to report pain. As a preliminary step towards the management of the pain, they need to be educated to understand the nature of pain, its treatment and their role in pain control. The education of patients and families involves a consistent effort by all interdisciplinary team members. Health care professionals should use the principles of adult education to guide patient and family teaching[1-4].

Table 7.1 provides an overview of the areas that need to be addressed when educating patients and families on cancer pain and its management.

Table 7.1 Patient Family Education

1. General Overview:
- Defining pain
    - Pain can be relieved
    - Concept of total pain
- Understanding the causes of pain
- Importance of early and appropriate treatment
- Talking to doctors and nurses about pain
    - How to describe pain
    - The use of pain rating scale

2. Pharmacological Management
- Overview- drug management of pain
    - Choice of drugs, appropriate dosing
    - How drugs are taken (e.g. regular dosing around-the-clock, titration, breakthrough drugs)
- Understanding and overcoming myths and fears
    - Addiction
    - Drug tolerance
    - Respiratory depression
- Controlling common side effects of drugs (e.g. nausea and constipation)

3. Non-pharmacological Management
- Role for non-pharmacological modalities
- Review of types of non-pharmacological management

Patients and family members should be educated using both verbal teaching and written materials. Verbal information about pain management may need to be reinforced frequently. It is important that all members of the health care team provide consistent information to patients and families. Written materials for cancer patients in Nova Scotia include pamphlets from Living Well with Cancer, and the Canadian Cancer Society and the *CCNS* Medication Info Sheets.

References:

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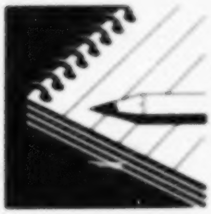
Part 8. Documentation

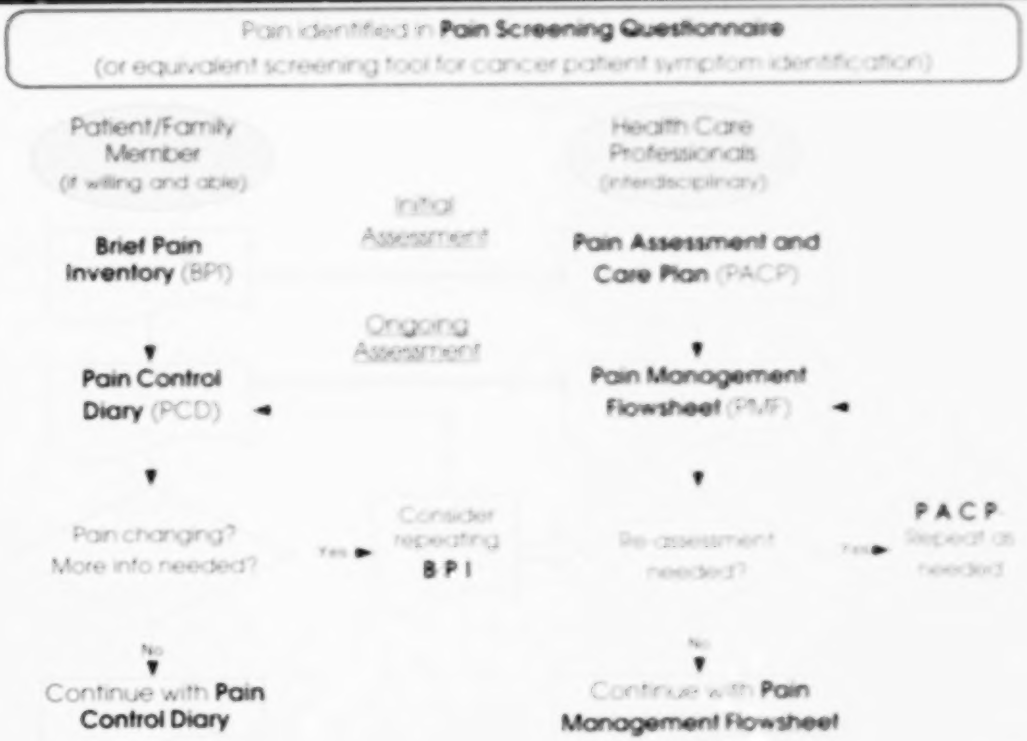


Accurate and ongoing assessment is crucial for the management of cancer pain. If pain is identified during a general assessment of any cancer patient, the pain should be further explored and documented using tools designed specifically to assess the many facets of the pain.

The forms in this section are recommended as the provincial standard tools for consistent pain assessment. At the initial assessment, and from time to time through the patient's pain experience, a thorough physical examination and medical history should be included, as well as a careful review of the many factors which contribute to the full experience of 'total pain'. The **Pain Assessment and Care Plan** (PACP- Form 8.2) is recommended for use by all health care professionals in any setting. The **PACP** may be used for documentation by different health care professionals on the same form, to aid in communication and consistency of approach. Between comprehensive assessments, pain should continue to be monitored. The **Pain Management Flowsheet** (Form 8.4) is suggested for ongoing monitoring by health care professionals. If there is any substantive change in pain, the PACP should be completed again, to document results from a thorough reassessment.

Ideally, pain assessment should begin with the patient and family. Some patients are willing and able to provide initial and ongoing self-assessment of their pain experience and their response to pain management. The **Brief Pain Inventory** (BPI-Form 8.1) is recommended for thorough assessment, and the **Pain Control Diary** (Form 8.3) for ongoing self-monitoring. Patients may choose to use their own diary for ongoing self-monitoring, if they prefer. If these tools are used by patients and/or families, the information is used to inform health care professionals about the patient's subjective pain assessments and experiences. The pathways and inter-relationships between measurement tools are described in the diagram below.

Figure 8.1 - Use of Pain Assessment Tools for Initial and Ongoing Assessment


Pain identified in **Pain Screening Questionnaire**
(or equivalent screening tool for cancer patient symptom identification)
Patient/Family Member
(if willing and able)
Health Care Professionals
(interdisciplinary)
Initial Assessment
Brief Pain Inventory (BPI)
Pain Assessment and Care Plan (PACP)
Ongoing Assessment
Pain Control Diary (PCD)
Pain Management Flowsheet (PMF)
Pain changing? More info needed?
Yes
Consider repeating **B P I**
Re-assessment needed?
Yes
P A C P- Repeat as needed
No
No
Continue with **Pain Control Diary**
Continue with **Pain Management Flowsheet**

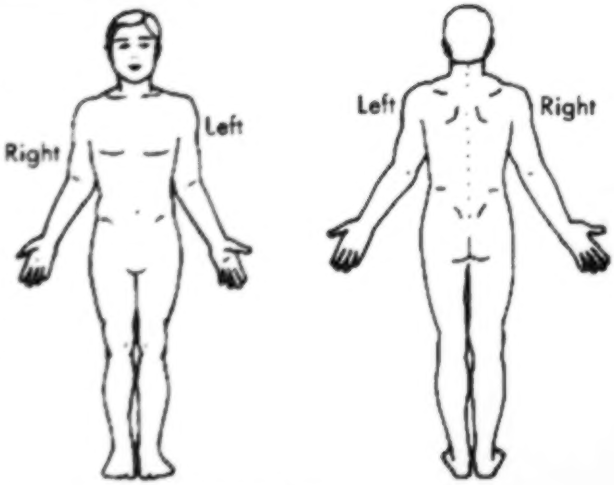
Cancer Care
Nova Scotia

Form 8.1

Brief Pain Inventory for Patients and Family

Name: ______________________________
Last First

Date: ____/____/____ Time:



1) On the picture, shade in the areas where you feel pain. Put an X on the area that hurts the most.

2) Please rate your pain: Circle the number for your **PAIN RIGHT NOW**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

3) Circle the number for your **WORST PAIN TODAY**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

4) Circle the number for your **LEAST PAIN TODAY**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

5) Circle the number for your **AVERAGE PAIN TODAY**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

over →

Brief Pain Inventory (continued)

6) **WHAT MEDICATIONS or TREATMENTS** are you receiving for your pain?

7) **HOW MUCH RELIEF** did the medications give you in the past 24 hours?

0% 10 20 30 40 50 60 70 80 90 100%
No relief
Complete relief

8) Circle the number for much **PAIN HAS INTERFERED or BOTHERED YOU**:

A. INTERFERED WITH GENERAL ACTIVITIES OF LIVING
0 1 2 3 4 5 6 7 8 9 10
Does not interfere
Completely interferes

B. INTERFERED WITH MOOD
0 1 2 3 4 5 6 7 8 9 10
Does not interfere
Completely interferes

C. INTERFERED WITH WALKING ABILITY
0 1 2 3 4 5 6 7 8 9 10
Does not interfere
Completely interferes

D. INTERFERED WITH NORMAL WORK (includes both work outside the home and housework)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere
Completely interferes

E. INTERFERED WITH RELATIONS WITH OTHER PEOPLE
0 1 2 3 4 5 6 7 8 9 10
Does not interfere
Completely interferes

F. INTERFERED WITH Sleep
0 1 2 3 4 5 6 7 8 9 10
Does not interfere
Completely interferes

G. INTERFERED WITH Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere
Completely interferes

Thank you. Please give this form to your doctor or nurse, to help with your pain control.

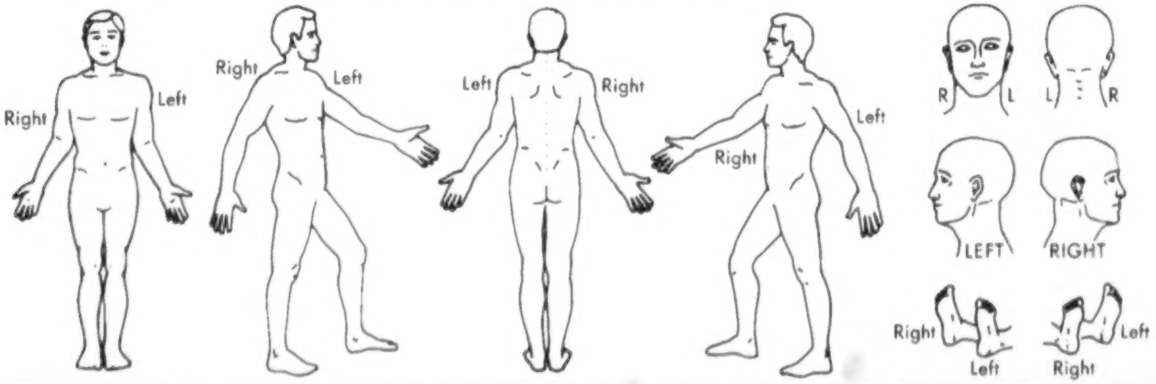
Cancer Care
Nova Scotia

Form 8.2

Pain Assessment and Care Plan

LOCATION(S) OF PAIN

Patient or health professional mark drawing. Number each site.



INTENSITY SCALE	
10	Worst Pain
9	
8	
7	
6	
5	Moderate
4	
3	
2	
1	
0	No Pain

PAIN PROFILE

Major Pain Location(1)		
Characteristics	Intensity (use 0 to 10) Present ☐	What makes the pain Better
Pattern[a]	Best ☐	Worse
	Worst ☐	Does it radiate? (Where?)
Other Pain Location(2)		
Characteristics	Intensity Present ☐	What makes the pain Better
Pattern[a]	Best ☐	Worse
	Worst ☐	Does it radiate? (Where?)
Other Pain Location(3)		
Characteristics	Intensity Present ☐	What makes the pain Better
Pattern[a]	Best ☐	Worse
	Worst ☐	Does it radiate? (Where?)

a. Pattern includes onset, duration, variations, timing of pain

Completed by:

Print Name____________________ Signature __________________ Date______________

ASSESSMENT OF TOTAL PAIN

HISTORY OF THE PAIN	UNDERSTANDING OF PAIN & TREATMENTS
PREVIOUS TREATMENTS & OUTCOMES	LEVEL OF MOBILITY, ADL, FUNCTION
CURRENT PAIN MEDICATIONS	COGNITIVE IMPAIRMENT
OTHER TREATMENTS FOR PAIN	SOCIAL HISTORY (& CULTURE)
SYMPTOMS ASSOCIATED WITH PAIN	FAMILY HISTORY
PSYCHOSOCIAL DISTRESS	PRACTICAL ISSUES

PHYSICAL ASSESSMENT OF PAIN

DIAGNOSTIC TESTS AND IMAGING

LABORATORY TESTS

PAIN DIAGNOSIS

GOALS OF PAIN THERAPY	INITIAL PAIN MANAGEMENT CARE PLAN
In the patient's own words Negotiated with the patient	

Cancer Care Nova Scotia

FORM 8.3

Pain Control Diary

Pain rating scale:
10 Worst Pain Ever
9
8
7
6
5 Moderate
4
3
2
1
0 No Pain

Name: ______________________

Date Started: ______________________

This is a record of where you are having pain, how much pain you have, and how your pain medicines are working. Please keep this record until you and your nurse/ doctor find the dose and frequency of medicine that provides satisfactory pain relief for you most of the time. After that, you only need to keep this record when you have problems related to your pain medicines.

The worst my pain has been is: ☐
(Enter number using pain rating scale)

At present I feel pain in the following areas:
(List all areas where pain is felt)

Date & Time	Site of Pain	Pain rating	Medicine I took	Did it work?	Any side effects?	Comments

Directions: Rate your pain before you take pain medicine and one to two hours later. This will let the doctor know if your current drugs are effective. When recording your pain, mark the rating for the pain at each site or area. (Continue on reverse side of page)

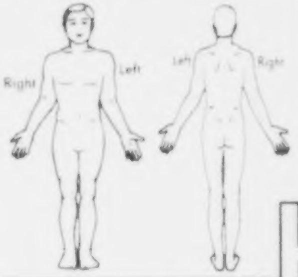
Date & Time	Site of Pain	Pain rating	Medicine I took	Did it work?	Any side effects?	Comments

Adapted from McCaffery M, Pasero C: *Pain: Clinical manual*, p. 87. Copyright © 1999, Mosby, Inc.

Cancer Care Nova Scotia

FORM 8.4

Pain Management Flowsheet



See baseline Pain Assessment and Care Plan- Date: ____________

	Intensity	Descriptor(s)
Major Pain Location(1)		
Other Pain Location(2)		
Other Pain Location(3)		

Patient Location:
Long Term Care ☐ Home Care ☐
Inpatient ☐ Ambulatory ☐ Office ☐

Pain rating scale:

10	Worst Pain Ever
9	
8	
7	
6	
5	Moderate
4	
3	
2	
1	
0	No Pain

Flowsheet Ratings

Date: ________ (yyyy/mm/dd)									
Time									
Current Pain Intensity:	10								
	9								
Regular Opioid AnalgesicOrder(s)	8								
	7								
	6								
	5								
	4								
Breakthrough Opioid Order(s)	3								
	2								
	1								
	0								
Scheduled Opioid dose ✓ Breakthrough Dose?: ✓									
# Doses Given # per Shift #per 24 hours									
Adjuvant Analgesics (list over) ✓									
Side Effects: Yes/No Constipation Nausea/Vomiting Sedation Other:									
Patient satisfied: Y or N									
Initials (✓ if patient self-rated)									

Flowsheet Ratings (continued)

Date: ____________ (yyyy/mm/dd)												
Time												
Current Pain Intensity:	10											
	9											
Regular Opioid Analgesic Order(s)	8											
	7											
	6											
	5											
	4											
Breakthrough Opioid Order(s)	3											
	2											
	1											
	0											
Scheduled Opioid dose	✓											
Breakthrough Dose?:	✓											
# Breakthrough Doses Given	# per Shift											
	#per 24 hours											
Adjuvant Analgesics (list below)	✓											
Side Effects: Yes/No	Constipation											
	Nausea/Vomiting											
	Sedation											
Other:												
Patient satisfied:	Y or N											
Initials (✓ if patient self-rated)												

Adjuvant Analgesics

Initials	Signature	Printed Name	Initials	Signature	Printed Name

Form 8.5

Cancer Care Nova Scotia

Sample patient agreement for opioid therapy

1. I, ______________________________ agree that

   Dr. ______________________________ will be the only doctor prescribing OPIOID (also known as NARCOTIC) pain medication for me. If my doctor is not available and another doctor who knows about my care is covering for my doctor, this doctor may prescribe an opioid for me in this circumstance.

2. I will obtain all of my prescriptions for opioids at one pharmacy. The exception would be an emergency situation or in the unlikely event that I run out of medication. Should such occasions occur, I will inform my doctor as soon as possible.

3. I will take the medication at the dose and frequency prescribed by my doctor. I agree not to increase the dose of opioid without first discussing it with my doctor.

4. I will attend all reasonable appointments, treatments and consultations as requested by my doctor. I agree that I will attend any appointment called by my doctor on short notice, to check that I am using my opioid only as ordered by my doctor.

5. I understand that the common side effects of opioid therapy include nausea, constipation, sweating and itchiness of the skin. Drowsiness may occur when starting opioid therapy or when increasing the dosage. I agree to refrain from driving a motor vehicle or operating dangerous machinery until such drowsiness disappears and my doctor agrees that I am fit to drive again.

6. I understand that using long-term opioids to treat pain may result in the development of a physical dependence on this medication, and that sudden decreases or discontinuation of the medication will lead to the symptoms of opioid withdrawal. I understand that opioid withdrawal is uncomfortable but not life-threatening.

7. I understand that there is a small risk that I may become addicted to the opioids I am being prescribed. As such, my doctor may require that I have additional blood, urine or hair testing and/or see a specialist in addiction medicine should a concern about addiction arise during my treatment.

8. I understand that the use of any mood-modifying substance, such as tranquillizers, sleeping pills, alcohol or illicit drugs (such as cannabis, cocaine, heroin or hallucinogens), can cause adverse effects or interfere with opioid therapy. Therefore I agree to refrain from the use of all of these substances without prior agreement from my doctor.

8. I agree to be responsible for the secure storage of my medication at all times. I agree not to give or sell my prescribed pain medication to any other person. Depending on the circumstances, lost medication may not be replaced until the next regular renewal date.

9. I consent to open communication between my doctor and any other health care professionals involved in my pain management, such as pharmacists, other doctors, emergency departments, etc.

10. I understand that if I break this agreement, my doctor reserves the right to stop prescribing opioid medications for me.

Date: ____________________

(Patient) ____________________

(Physician) ____________________

Adapted from: Jovey RD Ed., Managing Pain: The Canadian Healthcare Professional's Reference. Healthcare & Financial Publishing, Toronto, 2002

Part 9. Referral Information

Pain management may be offered by front-line health care professionals in any location. If assistance is required to help manage a patient with cancer-related pain, there are many resources, available in most health care districts. In the event that any front-line health care professional needs assistance to manage pain in a cancer patient, that caregiver may contact either the attending oncologist or the local pallitiave care service. Alternately, the district patient navigator may be contacted (provincial resource for districts without a patient navigator).

Referral of a cancer patient who needs help with pain management

To The Attending Oncologist:

Cape Breton Cancer Centre:

- Referrals to the Cape Breton Cancer Centre may be directed to the referrals/booking office at 902-567-7774 (fax 902-567-7911).
- For urgent or emergent referrals, please page the appropriate specialist on call through the Cape Breton Regional Hospital Locating service (902-567-8000) to discuss the referral.

Capital Health Cancer Care Program:

- Referrals to the QEII Health Sciences Centre- Cancer Care Program may be faxed to the Nova Scotia Cancer Centre referrals office at 902-473-6079 (tel. 902-473-6050 or 902-473-6098).
- Referral for patients with hematologic malignancies may be directed to the hematology referrals/booking office at 902-473-3447 (fax 902-473-3910).
- For urgent or emergent referrals, please page the appropriate specialist on call through the QEII HSC Locating service (902-473-2220) to discuss the referral.

To The District Palliative Care/Supportive Care Service:

South Shore Health:

- 902-634-7369 or 902-354-3436

South West Health:

- 902-742-3542 Ext. 414.

Annapolis Valley Health:

- 902-678-7381 Ext. 2270

Colchester East Hants Health Authority:

- 902-893-5554 Ext. 2306

Cumberland Health Authority:

- 902-667-5400 Ext. 6373

Pictou County Health:

- 902-752-7600 Ext. 4190

Guysborough Antigonish Strait Health Authority:

- 902-867-4296 or 902-867-4436

Cape Breton District Health Authority:

- 902-567-7846

Capital Health Cancer Care Program:

- 902-473-3119

For assistance with pediatric pain problem-

IWK Health Centre

- 902-470-7262

To The Cancer Patient Navigator:

- 1-866-524-1234 from anywhere in Nova Scotia.

Part 10. Practice Pathways

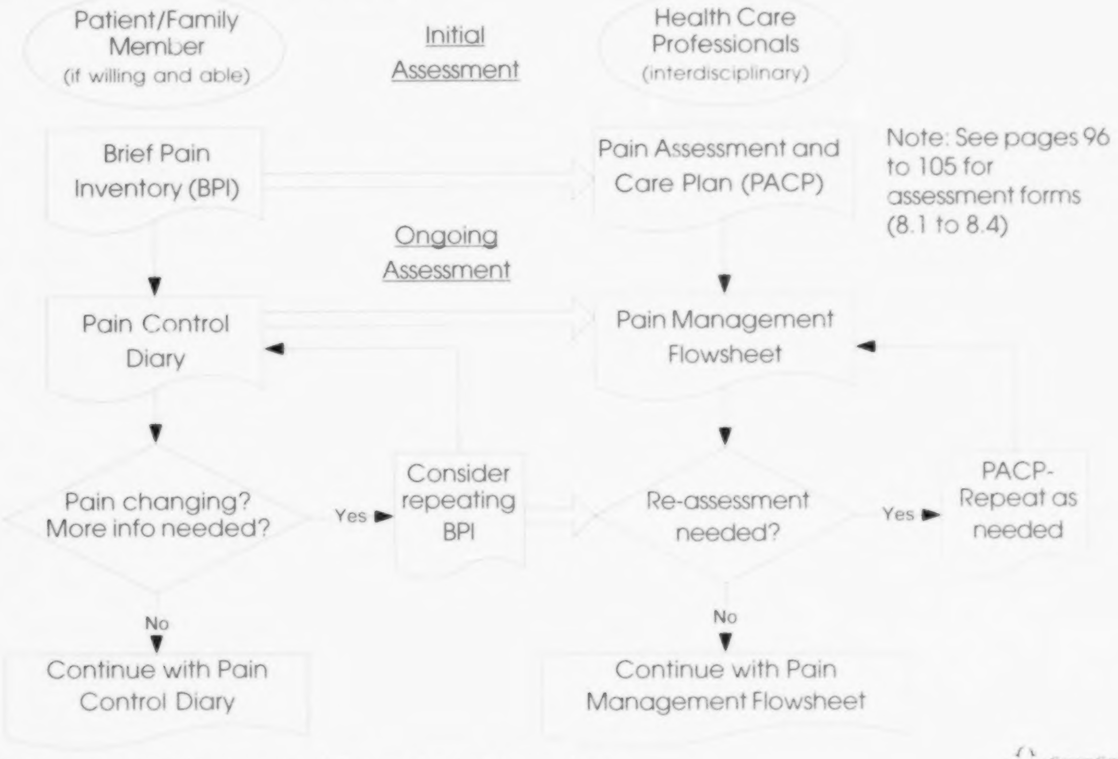
10.1 Assessment of Cancer Pain

Accurate assessment is crucial for the management of cancer pain. If pain is identified during a general assessment of any cancer patient, the pain should be further explored using tools designed specifically to assess the many facets of the pain.

Pain is a subjective experience, so assessment must include a subjective report of both the quantitative (e.g. pain intensity, locations) and qualitative (e.g. how the pain feels, how you are coping with the pain) pain experience. Many different scales have been used to measure pain intensity, but good evidence supports the use of a vertical 10 cm visual analog scale, with 0 to 10 graduations. This is the standard scale employed in the pain assessment forms recommended in this guideline.

Pain assessment should be consistent and should be performed regularly. Pain is not necessarily a static experience, and it can change over time. At the initial assessment, and from time to time through the patient's pain experience, a thorough physical examination and medical history should be included, as well as a careful review of the many factors which contribute to the full experience of 'total pain'. The **Pain Assessment and Care Plan** (Form 8.2) is recommended in the guideline as a tool for use by the health care professionals with thorough pain assessment, ensuring no important information is overlooked. Between thorough assessments, pain should continue to be monitored. The **Pain Management Flowsheet** (Form 8.4) is recommended for ongoing monitoring. If there is any substantive change in pain, a more thorough reassessment is recommended.

Pain assessment should begin with the patient and family whenever possible. Most patients are willing and able to provide initial and ongoing self-assessment of their pain experience and their response to pain management. Suggested tools for patients include the **Brief Pain Inventory** (Form 8.1) for thorough assessment, and the **Pain Control Diary** (Form 8.3) for ongoing self-monitoring. If these tools are used by patients and/or families, the information should be used by health care professionals for their pain assessments. The pathways and inter-relationships between measurement tools are described in the diagram below.


Patient/Family Member (if willing and able)
Initial Assessment
Health Care Professionals (interdisciplinary)
Brief Pain Inventory (BPI)
Pain Assessment and Care Plan (PACP)
Note: See pages 96 to 105 for assessment forms (8.1 to 8.4)
Ongoing Assessment
Pain Control Diary
Pain Management Flowsheet
Pain changing? More info needed?
Yes
Consider repeating BPI
Re-assessment needed?
Yes
PACP- Repeat as needed
No
No
Continue with Pain Control Diary
Continue with Pain Management Flowsheet

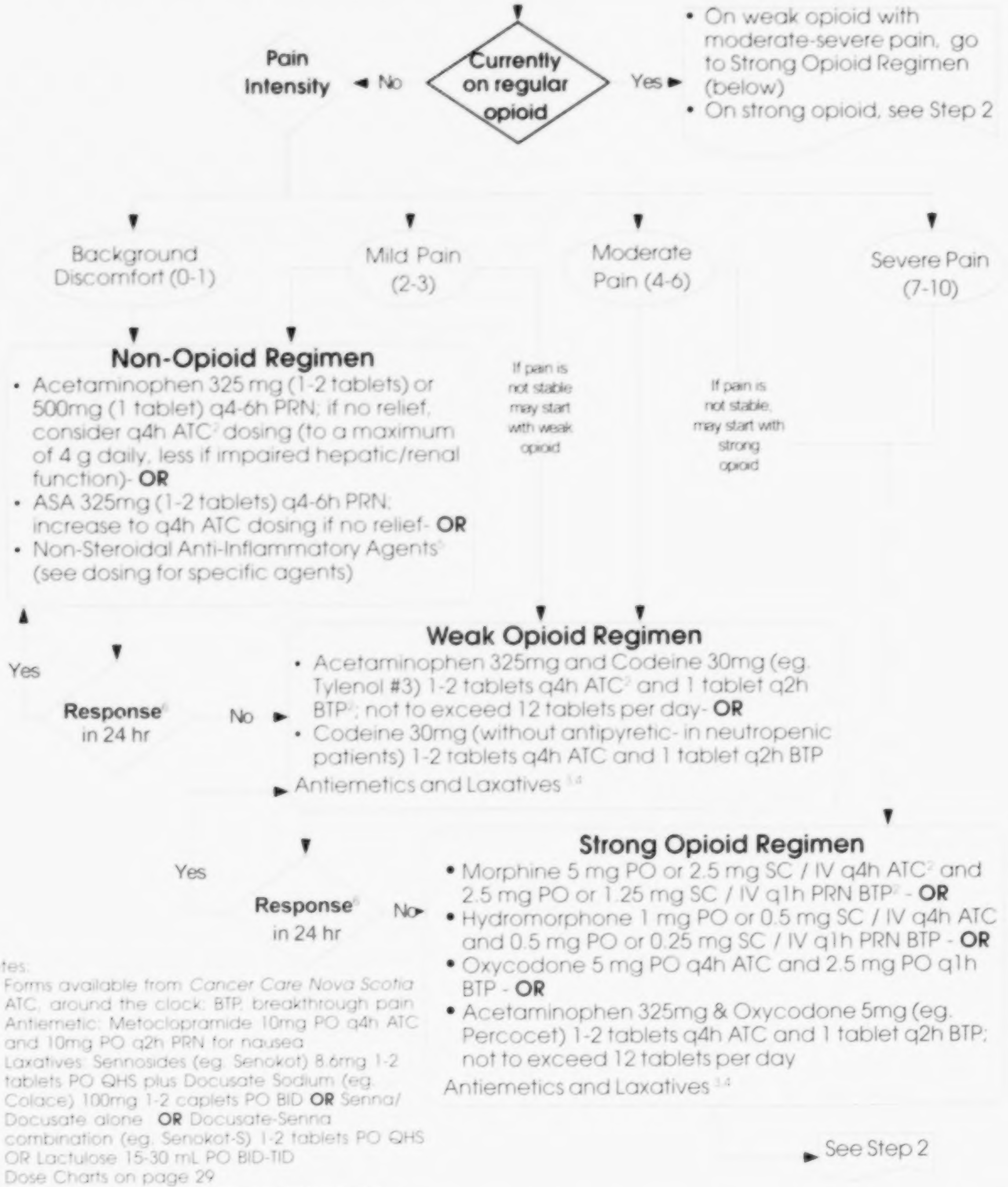
10.2 Treatment of Cancer Pain - Step 1

Pain Assessment

Complete **Pain Assessment and Care Plan** (Form 8.3[1]), including:

- Assess all causes of pain (total pain).
- Determine pain location(s), pain intensity, and other symptoms.
- Complete full history and physical exam
- Document all previous analgesics (including opioids) and response to each

Consider renal function (eg. BUN, creatinine, electrolytes, Ca^{2+}), hepatic function (eg. transaminases, LDH), CBC, albumin



Currently on regular opioid
No
Pain Intensity
Yes
Background Discomfort (0-1)
Mild Pain (2-3)
Moderate Pain (4-6)
Severe Pain (7-10)
If pain is not stable may start with weak opioid
If pain is not stable, may start with strong opioid
Yes
Response[6] in 24 hr
No
Yes
Response[6] in 24 hr
No

- On weak opioid with moderate-severe pain, go to Strong Opioid Regimen (below)
- On strong opioid, see Step 2

Non-Opioid Regimen

- Acetaminophen 325 mg (1-2 tablets) or 500mg (1 tablet) q4-6h PRN; if no relief, consider q4h ATC[2] dosing (to a maximum of 4 g daily, less if impaired hepatic/renal function)- **OR**
- ASA 325mg (1-2 tablets) q4-6h PRN; increase to q4h ATC dosing if no relief- **OR**
- Non-Steroidal Anti-Inflammatory Agents[5] (see dosing for specific agents)

Weak Opioid Regimen

- Acetaminophen 325mg and Codeine 30mg (eg. Tylenol #3) 1-2 tablets q4h ATC[2] and 1 tablet q2h BTP[2]; not to exceed 12 tablets per day- **OR**
- Codeine 30mg (without antipyretic- in neutropenic patients) 1-2 tablets q4h ATC and 1 tablet q2h BTP

► Antiemetics and Laxatives[3,4]

Strong Opioid Regimen

- Morphine 5 mg PO or 2.5 mg SC / IV q4h ATC[2] and 2.5 mg PO or 1.25 mg SC / IV q1h PRN BTP[2] - **OR**
- Hydromorphone 1 mg PO or 0.5 mg SC / IV q4h ATC and 0.5 mg PO or 0.25 mg SC / IV q1h PRN BTP - **OR**
- Oxycodone 5 mg PO q4h ATC and 2.5 mg PO q1h BTP - **OR**
- Acetaminophen 325mg & Oxycodone 5mg (eg. Percocet) 1-2 tablets q4h ATC and 1 tablet q2h BTP; not to exceed 12 tablets per day

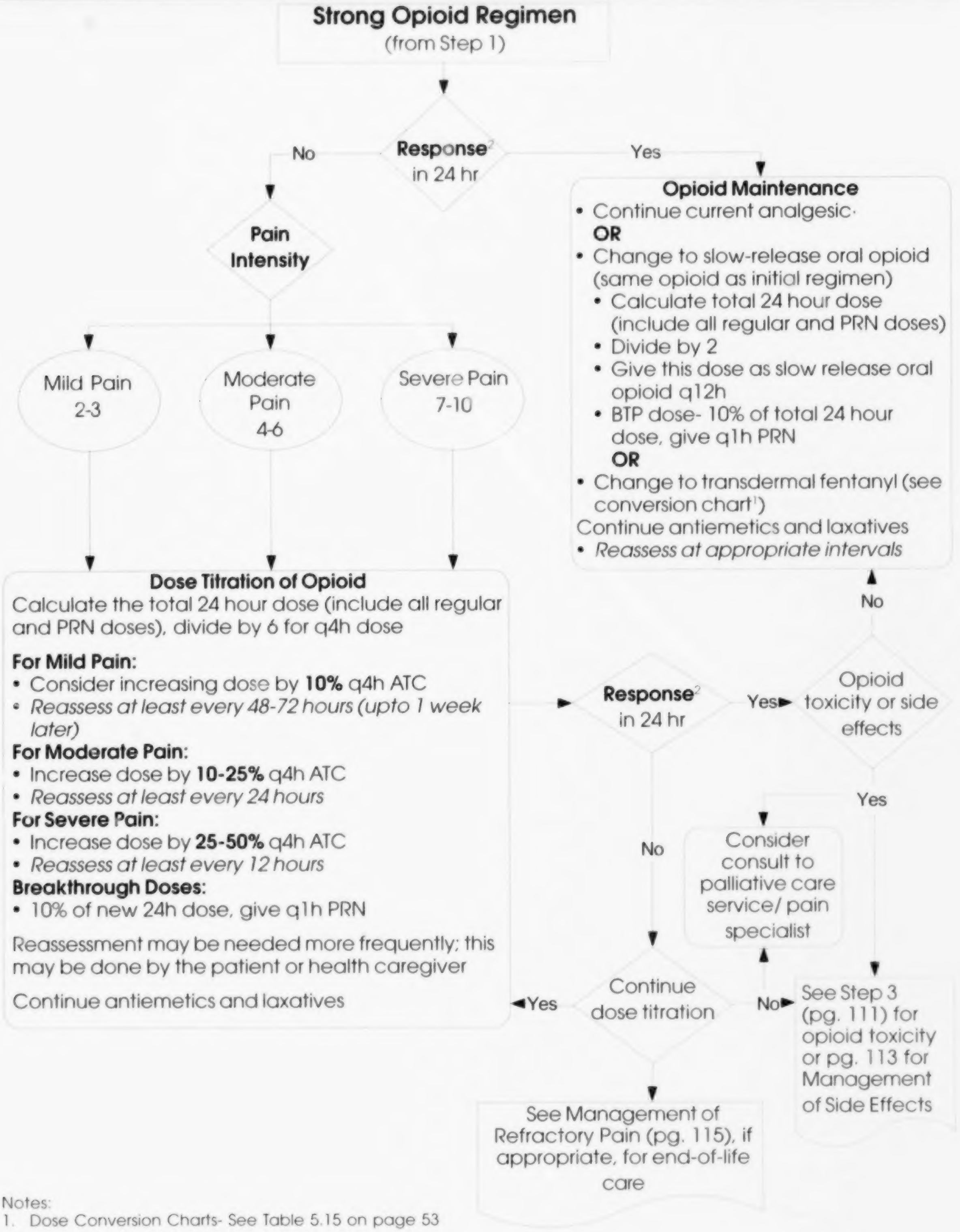
Antiemetics and Laxatives[3,4]

► See Step 2

Notes:

1. Forms available from *Cancer Care Nova Scotia*
2. ATC, around the clock; BTP, breakthrough pain
3. Antiemetic: Metoclopramide 10mg PO q4h ATC and 10mg PO q2h PRN for nausea
4. Laxatives: Sennosides (eg. Senokot) 8.6mg 1-2 tablets PO QHS plus Docusate Sodium (eg. Colace) 100mg 1-2 caplets PO BID **OR** Senna/ Docusate alone **OR** Docusate-Senna combination (eg. Senokot-S) 1-2 tablets PO QHS OR Lactulose 15-30 mL PO BID-TID
5. Dose Charts on page 29
6. Response refers to acceptable pain control

10.3 Treatment of Cancer Pain - Step 2



Strong Opioid Regimen
(from Step 1)

Response[2] in 24 hr

Pain Intensity

Mild Pain 2-3

Moderate Pain 4-6

Severe Pain 7-10

Opioid Maintenance
- Continue current analgesic
OR
- Change to slow-release oral opioid (same opioid as initial regimen)
  - Calculate total 24 hour dose (include all regular and PRN doses)
  - Divide by 2
  - Give this dose as slow release oral opioid q12h
  - BTP dose- 10% of total 24 hour dose, give q1h PRN
  OR
- Change to transdermal fentanyl (see conversion chart[1])

Continue antiemetics and laxatives
- *Reassess at appropriate intervals*

Dose Titration of Opioid
Calculate the total 24 hour dose (include all regular and PRN doses), divide by 6 for q4h dose

For Mild Pain:
- Consider increasing dose by **10%** q4h ATC
- *Reassess at least every 48-72 hours (upto 1 week later)*

For Moderate Pain:
- Increase dose by **10-25%** q4h ATC
- *Reassess at least every 24 hours*

For Severe Pain:
- Increase dose by **25-50%** q4h ATC
- *Reassess at least every 12 hours*

Breakthrough Doses:
- 10% of new 24h dose, give q1h PRN

Reassessment may be needed more frequently; this may be done by the patient or health caregiver

Continue antiemetics and laxatives

Response[2] in 24 hr

Opioid toxicity or side effects

Consider consult to palliative care service/ pain specialist

Continue dose titration

See Step 3 (pg. 111) for opioid toxicity or pg. 113 for Management of Side Effects

See Management of Refractory Pain (pg. 115), if appropriate, for end-of-life care

Notes:
1. Dose Conversion Charts- See Table 5.15 on page 53
2. Response refers to acceptable pain control

10.4 Treatment of Cancer Pain - Step 3

Opioid toxicity or side effects[1]

Opioid Rotation

Opioid rotation is changing from one opioid to another opioid. Opioid rotation may be considered if pain is or has been relieved with original opioid, but actual or predicted toxicity limits further dose titration.

- Select an alternate opioid
- Calculate equianalgesic equivalent dose of new opioid- See Conversions (below)
- Adjust starting dose of new opioid-consider decreasing initial dose by 25-50% if pain controlled by old opioid (no reduction if pain not controlled by old opioid)
- Titrate dose, as in Step 2

Dose Conversion Table for Opioids

Drug	Oral Dose	Parenteral Dose	Ratio PO to SC	Ratio PO to Morphine PO
Morphine	20 (-30) mg	10 mg	2 : 1	1 : 1
Hydromorphone	4 (-6) mg	1 mg	2 : 1	1 : 5
Oxycodone (controversial)	15 - 30 mg	20 mg	1-1.5:1	1:1 to 1:2
Codeine	200 mg	120 mg	2 : 1	12 : 1
Fentanyl	For conversion to transdermal dose, see Transdermal Fentanyl Dosing Table - Page 114			
Methadone	For conversion, see Dosing of Oral Methadone - Page 114			

NOTE: It is strongly recommended that Meperidine (Demerol), Pentazocine (Talwin) or Propoxyphene (Darvon) **NOT** be used for cancer pain management

Management Options[2]

Addition of Adjuvant(s)

Adjuvant agents may be considered to augment the analgesic effect of an opioid, or to produce analgesia by a different mechanism. Adjuvant agents may be considered for malignant bone pain, neuropathic pain, incident pain, pain from compression or distension of tissues, or other related pain problems.

- Adjuvant analgesic agents and doses are described on page 117

Opioid Dose Reduction

Reduction of dose may be considered instead of opioid rotation if it is suspected that the opioid toxicity is due to excessive dosage and pain may be controlled with a lower dose.

- Careful dose reduction may eliminate opioid toxicity- Monitor pain control
- Dose reduction may include the concurrent addition of adjuvant analgesics

Consider consult to palliative care service/ pain specialist

Change Route of Opioid

Sometimes changing the route of administration may reduce toxicity or side effects. Consider changing administration route if there are absorption concerns or if the oral route is limited by symptoms (eg. nausea or vomiting). Choice of alternate route is a clinical decision.

- Routes of administration include oral (recommended first choice), rectal or parenteral (eg. subcutaneous, intravenous), transmucosal (eg. sublingual/buccal, nasal) or transdermal.

Manage Side Effects or Opioid Toxicities ► See Management of Side Effects from Opioid Therapy- Page 113

NOTES

1. Opioid toxicity refers to symptoms related to opioid dose (eg. neurological symptoms) whereas side effects are symptoms which may occur at any opioid dose (eg. constipation). see full version for more details
2. See full version of the guideline for discussion of management options and criteria for selection

10.5 Opioid Dose Conversions

Dosing of Transdermal Fentanyl

- To convert from an opioid to transdermal fentanyl (Duragesic), first calculate the 24 hour oral morphine equivalent dose, then locate the equivalent fentanyl dose on the chart below
- Continue the original opioid for 12-24 hours after the first transdermal patch is applied, to allow the patch to create a reservoir under the skin

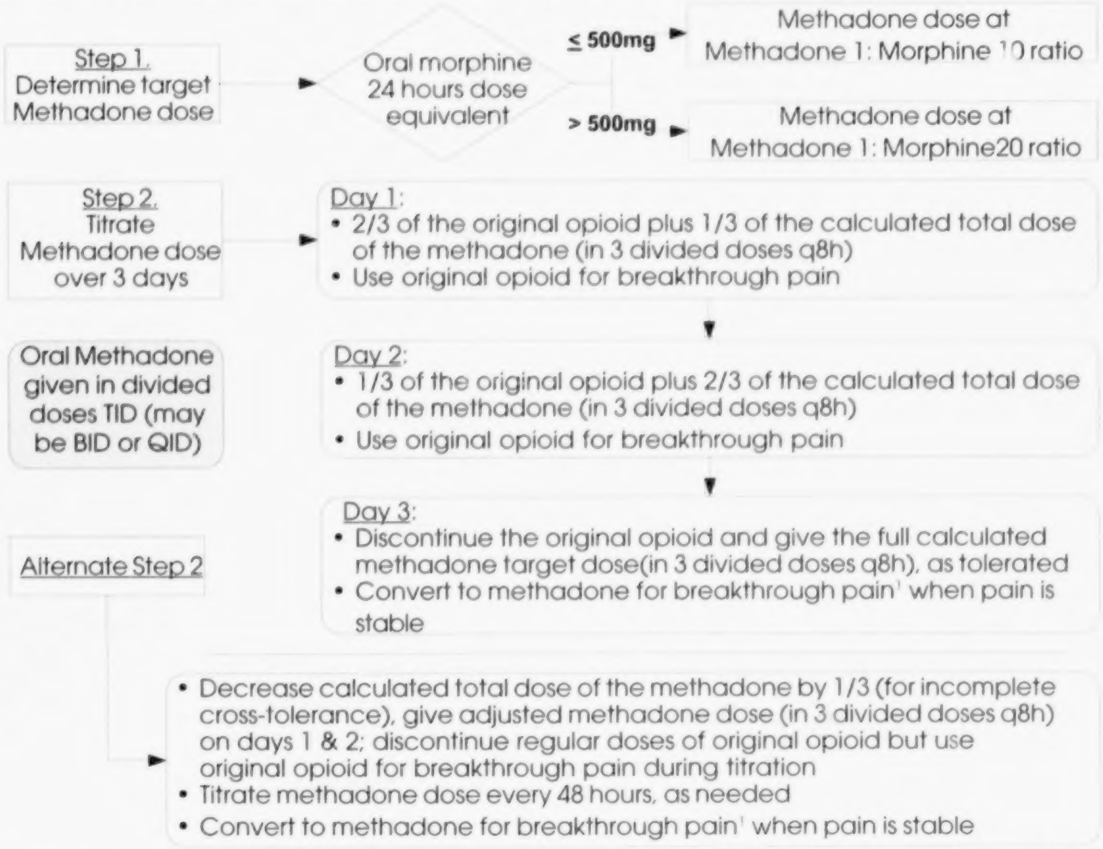
Transdermal Fentanyl Dose Conversion from Morphine

Oral Morphine Dose per 24 hrs.	Parenteral Morphine Dose per 24 hrs.	Fentanyl Patch Dose (mcg/hr)
45-134 mg	15-44 mg	25
135-224 mg	45-74 mg	50
225-314 mg	75-104 mg	75
315-404 mg	105-134 mg	100
405-494 mg	135-164 mg	125
495-584 mg	165-194 mg	150

- For ease of conversion, consider 50-100 mg of oral morphine in 24 hours equal to 25mcg/hr transdermal fentanyl
- Breakthrough opioid medication- use 5-10 mg morphine/ 1-2 mg hydromorphone q1 hr PRN for each 25 mcg/hr fentanyl

Dosing of Oral Methadone for Cancer Pain

- Prescribers are required to have a methadone licence (from Health Canada) to prescribe this agent
- It is suggested to consult with a prescriber with methadone expertise when considering the use of methadone
- Equianalgesic conversion ratios from other opioids to methadone may vary based upon the dose of the opioid at time of conversion
- There are several methods for converting from another opioid to methadone.



Step 1.
Determine target Methadone dose

Oral morphine 24 hours dose equivalent

≤ 500mg → Methadone dose at Methadone 1: Morphine 10 ratio

> 500mg → Methadone dose at Methadone 1: Morphine20 ratio

Step 2.
Titrate Methadone dose over 3 days

Day 1:
- 2/3 of the original opioid plus 1/3 of the calculated total dose of the methadone (in 3 divided doses q8h)
- Use original opioid for breakthrough pain

Day 2:
- 1/3 of the original opioid plus 2/3 of the calculated total dose of the methadone (in 3 divided doses q8h)
- Use original opioid for breakthrough pain

Day 3:
- Discontinue the original opioid and give the full calculated methadone target dose(in 3 divided doses q8h), as tolerated
- Convert to methadone for breakthrough pain[1] when pain is stable

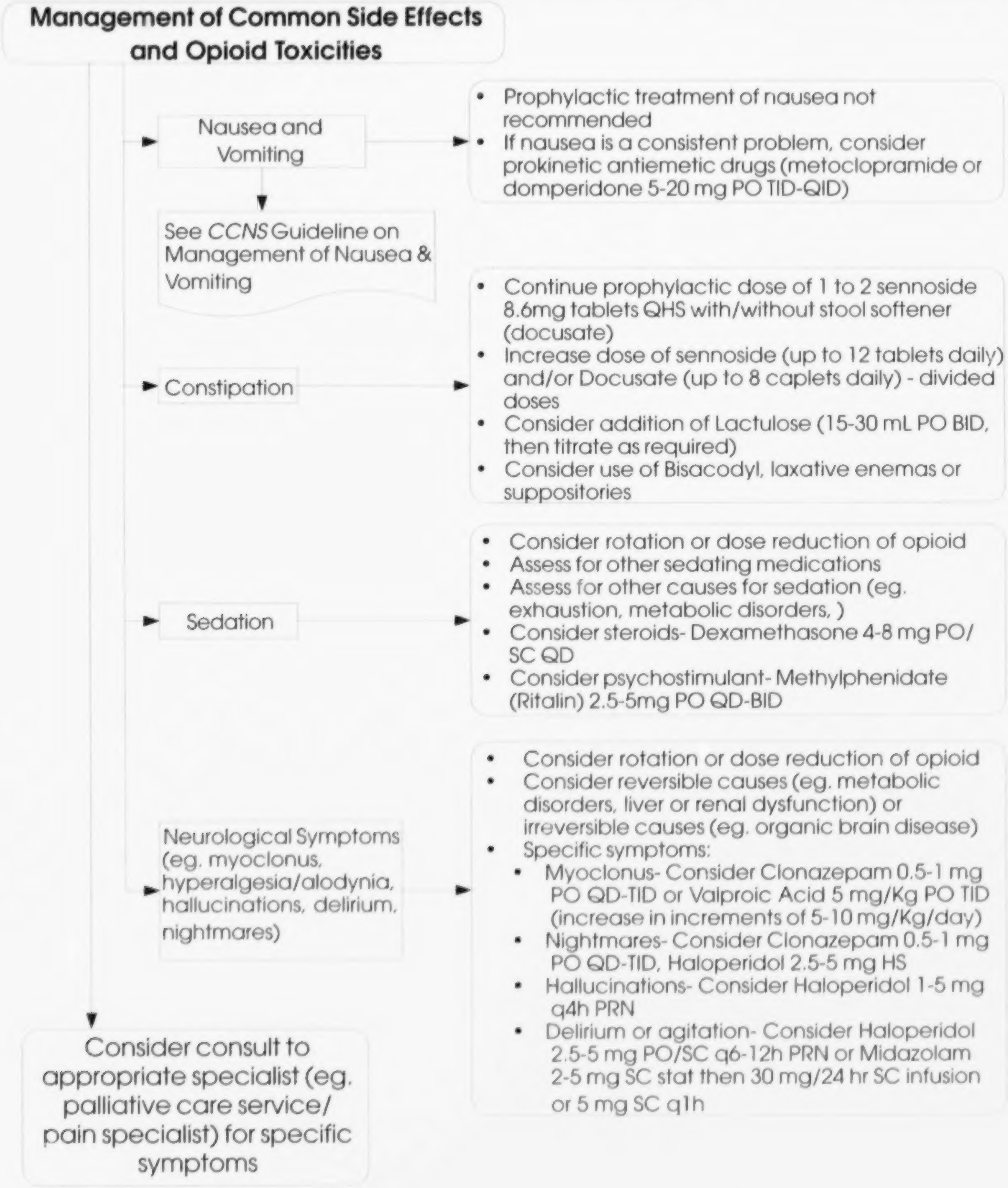
Oral Methadone given in divided doses TID (may be BID or QID)

Alternate Step 2

- Decrease calculated total dose of the methadone by 1/3 (for incomplete cross-tolerance), give adjusted methadone dose (in 3 divided doses q8h) on days 1 & 2; discontinue regular doses of original opioid but use original opioid for breakthrough pain during titration
- Titrate methadone dose every 48 hours, as needed
- Convert to methadone for breakthrough pain[1] when pain is stable

1.Consider 10% of total daily methadone dose given q2-3h for breakthrough pain

10.6 Management of Side Effects/Toxicities from Opioid Therapy



Management of Common Side Effects and Opioid Toxicities

Nausea and Vomiting

- Prophylactic treatment of nausea not recommended
- If nausea is a consistent problem, consider prokinetic antiemetic drugs (metoclopramide or domperidone 5-20 mg PO TID-QID)

See *CCNS* Guideline on Management of Nausea & Vomiting

Constipation

- Continue prophylactic dose of 1 to 2 sennoside 8.6mg tablets QHS with/without stool softener (docusate)
- Increase dose of sennoside (up to 12 tablets daily) and/or Docusate (up to 8 caplets daily) - divided doses
- Consider addition of Lactulose (15-30 mL PO BID, then titrate as required)
- Consider use of Bisacodyl, laxative enemas or suppositories

Sedation

- Consider rotation or dose reduction of opioid
- Assess for other sedating medications
- Assess for other causes for sedation (eg. exhaustion, metabolic disorders,)
- Consider steroids- Dexamethasone 4-8 mg PO/ SC QD
- Consider psychostimulant- Methylphenidate (Ritalin) 2.5-5mg PO QD-BID

Neurological Symptoms (eg. myoclonus, hyperalgesia/alodynia, hallucinations, delirium, nightmares)

- Consider rotation or dose reduction of opioid
- Consider reversible causes (eg. metabolic disorders, liver or renal dysfunction) or irreversible causes (eg. organic brain disease)
- Specific symptoms:
  - Myoclonus- Consider Clonazepam 0.5-1 mg PO QD-TID or Valproic Acid 5 mg/Kg PO TID (increase in increments of 5-10 mg/Kg/day)
  - Nightmares- Consider Clonazepam 0.5-1 mg PO QD-TID, Haloperidol 2.5-5 mg HS
  - Hallucinations- Consider Haloperidol 1-5 mg q4h PRN
  - Delirium or agitation- Consider Haloperidol 2.5-5 mg PO/SC q6-12h PRN or Midazolam 2-5 mg SC stat then 30 mg/24 hr SC infusion or 5 mg SC q1h

Consider consult to appropriate specialist (eg. palliative care service/ pain specialist) for specific symptoms

10.7 Management of Pain Crisis

Pain crisis may occur with any patient at any point in time. Pain crisis is acute, severe pain which is overwhelming and exceeds the coping strategies of the patient and family. As a crisis, there is no time for the usual dose titration. Pain crisis is an **emergency** situation.

Identification of Pain Crisis

1. Patient/family call
2. Telephone assessment and advice to patient (by attending physician or nurse to determine if crisis and to suggest immediate measures until visit)

Calls may be to:

1. Family doctor or other attending physician or nurse
   - After hours- call physician, if on-call available
2. Palliative care or oncology service, if attending with this service
   - After hours- call service , if on-call available
3. Emergency room- only if no other call is available

Patient Visit

- Urgent visit- arrange as soon as possible (do not defer)
- Preferably within 1 to 2 hours of call

Assessment

- Assess pain level and recent history (including medications)
- Assess distress level and recent history of distress

Treatment of Pain Crisis

Manage BOTH pain and distress

New Pain Syndrome

Identify any specific syndromes (e.g. spinal cord compression, SVC syndrome)

- Treat as per guidelines appropriate to specific syndrome(s)

Exacerbation of Underlying Pain

- No new pain pathology
- Rapid titration of short-acting opioid (e.g. Morphine 5-10 mg or Hydromorphone 1-2 mg SC/IV -not PO; repeat q10 min PRN for ongoing severe pain)
- Titrate until pain relief or sedation

Distress

- Anxiolytic agent for acute distress (parenteral route preferred)
- Treatment plan per *CCNS* Distress Management Guideline

EXAMPLE

- Calculate the total 24 hour opioid dose (include all regular and PRN doses), increase by 25-50%, divide by 6, convert to parenteral equivalent (usually 50% of oral dose); Give this as a bolus opioid dose SC and give lorazepam 0.5-1 mg SC or midazolam 1mg (up to 5 mg) SC for immediate distress management
- Repeat doses of both opioid and anxiolytic agent q30 minutes until pain relief or sedation intervenes
  - Maximum 3 doses of each agent- if no relief, re-assess and consider palliative care/pain specialist consultation
- Caution- monitor respiratory rate, and SaO_2 (if available)
  - If respiratory depression with low O_2 saturation, adminster O_2, provide verbal & tactile stimulation; if inadequate response consider giving low dose naloxone (0.4 mg diluted in saline to 10 mL, give 1 mL q1-2 minutes until adequate SaO_2)

Follow-Up

- Consider admission to hospital until pain crisis is stabilized (unless patient is actively dying or wishes to remain at home)
- When pain crisis is stabilized, recalculate new q4h dosing of opioid
- Reassess within 24 hours of stabilization of pain crisis; educate patient/family on new expectations
- Refer to appropriate other services for long-term distress management

10.8 Management of Refractory Pain (Palliative Sedation)

Refractory pain is pain that is not adequately controlled despite aggressive efforts to identify and provide a tolerable therapy in a timely fashion, that does not compromise consciousness. This is pain that is intolerable, unbearable and intractible. Refractory pain must be distingushed from difficult pain, which is pain that has not been managed with usual efforts and requires aggressive intensive efforts for a timely effect. Palliative sedation, the induction of light-to-deep sleep with sedative drugs, is one option to manage refractory pain when all other options have been exhausted in end-of-life patients.

Identify Refractory Pain by the Health Care Professional

- Patient continues to report ongoing, intolerable pain despite aggressive therapy
- Differential diagnosis to exclude difficult pain syndrome
- All efforts to control pain have been adequately explored
- Pain control efforts that cannot be achieved within a reasonable time, relative to the patient's prognosis and expectations, are ruled out

Assessment of Refractory Pain

- Use assessment tools for cancer pain (see Assessment of Cancer Pain); increase frequency of assessments
- Consult with other sub-specialists to ensure that all reasonable efforts to manage pain have been taken

Decision to Offer Palliative Sedation

- Involve the patient/family, the interdisciplinary team and, if necessary, the ethics team
- Palliative sedation should ONLY by offered by a consultation service, or a team which includes at least two physicians; other disciplines (e.g. nursing, spiritual care, social work) will be involved during treatment
- Review the ethics of palliative sedation with the patient/family, including the seriousness of the prognosis, the lack of alternative options for pain relief, short life expectancy, and the intention is to relieve suffering/pain but not to hasten death
  - Consultation by an ethics committee is recommended when there is conflict about the decision
- Explain all treatment options to the patient/family, negotiate the terms of sedation (e.g. continuous, intermittent, periodic, on demand)
- **Obtain informed patient consent** (or surrogate, only if the patient is incompetent); document on the health record

Management of Palliative Sedation

- Select a treatment option, which is available for the treatment setting
- Monitor patient's pain, respiratory rate and consciousness regularly; review with physician at least every 24 hours
- Physician to titrate sedative medications to meet the treatment goals, do not order dose ranges
- Maintain previous opioid therapy (may be able to reduce dosage)

OPTIONS FOR PALLIATIVE SEDATION

Start at low dose and titrate to effect:

- Midazolam 1-7 mg/hr SC/IV infusion (drug of choice)
- Lorazepam 1-4 mg SC q4-6h
- Methotrimeprazine 5-25 mg SC q4h (only option with analgesic effects)
- Haloperidol 2-10 mg SC q4h
- Propofol 0.5-7 mg/hr IV infusion (NB. general anesthetic with rapid onset and elimination- may be restricted in some hospitals)
- May add breakthrough doses of same drug as needed

10.9 Management of Special Pain Problems

Pain Treatment in Substance Abusers

Identify Patients at High Risk of Substance Abuse

Consider consult to appropriate specialist (eg. palliative care service/ pain specialist)

Assessment

- In addition to usual pain assessment consider a thorough history to include:
  - Alcohol, drugs and tobacco use (consider CAGE Questionnaire)
  - Compulsive behaviors (e.g. gambling)
  - Mental health issues
  - Social supports or systems
  - Previous criminal record (patient and family)
- Correlation to physical exam results
- Consider drug screening tests

Pain Treatment

- Treat the cancer pain
- Higher doses of opioids will be necessary for cancer pain control in patients who are substance abusers
- Consider using methadone or fentanyl patches, optimize adjuvants
- Develop a contract with the patient (see Form 8.5)
- Compliance monitoring crucial
- Consider prescribing small supplies or daily supply of opioids, notification of pharmacies and narcotic monitoring system
- Consider use of tamper-proof medication containers
- Consider unplanned visits to screen for drug use (include in contract)
- Report to police any questionable activities (which could be drug diversion)

Follow-up Practices

- Regular follow-up visits to ensure compliance with contract
- Ensure pain relief is addressed

Spasms (cramps)

For muscular or skeletal spasms:

- Baclofen 5 mg PO TID (may titrate q3d up to 20 mg PO TID)
- Diazepam 2 mg PO TID (may titrate up to 10 mg PO TID
- Midazolam 1-3 mg SC q30 min PRN (or lorazepam 0.5-2 mg SC q1 hr PRN)

For visceral spasms or cramps:

- Loperamide 1-2 mg PO TID to QID
- Buscopan (hyoscine butylbromide) 10 mg PO TID-QID
- Scopolamine patch 1.5 mg transdermally q3d
- Glycopyrrolate 0.2-0.4 mg SC q4-8h
- Consider Octreotide 200 mcg SC q8h (may increase to 800 mcg)

10.9 Management of Special Pain Problems- 2

Post-Radiation Pain

Acute Pain Problems (e.g. burns)

- Most radiation-induced pain responds to usual opioid therapy; see Steps 1 & 2 (pages 108-109)
- If severe, consult with radiation oncologist for management

Pain Flares

- Rapid upward titration of opioid when pain increases
- Careful monitoring, decrease opioids when pain decreases

Chemotherapy-Related Pain Syndromes

Drug-Related Neuropathies

- Consult with oncologist (chemotherapy may be altered)
- Treatment like neuropathic pain (see page 117)
- Educate patient/family
- Explore psychosocial support groups, complementary treatment options

Hand-Foot Syndrome (Palmar-Plantar Erythrodysesthesia)

- Consult with oncologist (chemotherapy may be altered)
- Symptomatic relief with topical moisturizing creams (e.g. BagBalm, Udder Cream)

Mucositis Pain

- See ***CCNS* Guidelines for the Management of Oral Complications from Cancer Therapy**

Chronic Pain in Cancer Patients

- Cancer patients may also suffer from pain due to other causes
- Treat each type of pain, as appropriate
- Pain may be due to cancer treatment (e.g. surgery, radiation therapy)
- Consider referral to appropriate sub-specialist (e.g. gastroenterology, neurology, urology, ENT), or pain specialist
- Consider non-pharmacological approach (e.g. physiotherapy, nerve blocks, TENS, distraction methods, guided imagery)
- Consider appropriate support groups

10.10 Adjuvant Therapies

In addition to optimal opioid therapy and cancer treatment, if appropriate

Malignant Bone Pain ►

Acetaminophen 325-650 mg q4h PO
- To a maximum of 4 g/day *(less with renal or hepatic impairment)*.

AND/OR

Non-Steroidal Anti-Inflammatory Agent PO (NSAID)
- Common Examples:
  - Ibuprofen 200-800 mg TID (available without prescription)
  - Naproxen 250-500 mg BID
  - Diclofenac 25-50 mg TID or 75 mg SR daily
  - Celecoxib 100-200 mg QD-BID
- May co-administer cytoprotectant agent (eg. Misoprostol) in patients with risk of ulceration or concurrently on NSAIDs and steroids

AND/OR

Corticosteroid
- Dexamethasone 4 mg PO qAM (may use higher or lower doses)
- May be added to NSAID/Acetaminophen, or replace NSAID
- Use cytoprotectant if corticosteroid and NSAID given concurrently
- Plan use for limited period, monitor for effects; taper dose to discontinue

AND/OR

Bisphosphonate
- Pamidronate 60-90 mg IV or Zoledronic Acid 4-8 mg IV every 3-4 weeks

AND/OR

Non-Pharmacologic Approaches:
Consider radiotherapy, physiotherapy, prophylactic subluxation, or fixation (if fracture present)

Neuropathic Pain[1] ►

Tricyclic Antidepressant
- Amitriptyline 10 to 25 mg qHS
- Nortriptyline 10 to 25 mg qHS or Desipramine 25 mg qHS *(fewer anticholinergic side effects)*.

AND/OR

Antiepileptic drugs
- Gabapentin 100-300 mg qHS
- Carbamazepine 100-200 mg BID
- Valproate 250 mg daily to TID

AND/OR

Corticosteroid (as above)

AND/OR

Ketamine 5-10 mg PO BID (refer to pain specialist for initiation and titration)

AND/OR

Non-Pharmacologic Approaches:
Consider radiotherapy, surgical decompression, TENS, nerve blocks

Note: drug listings are examples with suggested starting doses

Incident Pain (Pain on mobilization) ►

Sufentanil 25-50 mcg SL/buccal, **Fentanyl** 50 mcg SL/buccal prior to mobilization

Non-Pharmacologic Approaches:
- Sling, splint, crutches, cane, walker, physiotherapy/occupational therapy

Pain from Compression or distention of tissues ►

Corticosteroid (as above)

AND/OR

Non-Pharmacologic Approaches: Consider radiotherapy, surgical decompression

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[1] Methadone may be a more effective opioid in neuropathic pain treatment

See: Table 5.22 for more details on drug dosing

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